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The Relation of the Theca-Cells to Disturbances of the Menstrual Cycle

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INTRODUCTION.

IN a previous paper[1] it has been shown that when the theca-cells surrounding follicles of the baboon ovary proliferate or luteinize sufficiently extensively and are visible to the naked eye as yellowish plaques or masses, there is often an accompanying disturbance in the menstrual cycle in the form of bleeding, amenorrhoea, singly or in combination.

The literature contains numerous references to an analogous relation between thecal proliferations and menstrual irregularities in the human[2], but because these yellow masses of theca-cells are invariably related to atretic or cystic follicles, structures which by themselves are known to produce menstrual upsets, these theca-cells alone have been disregarded as significant in the production of such disturbances. The recent interest in the so-called rare tumours of the ovary, particularly the theca-cell tumours, has led to much speculation concerning the endocrine effects of the various components of the normal ovary. Originally oestrogen was believed to arise only from granulosa-cells. Then Zondek suggested that the theca-cells elaborated greater quantities of oestrogen than did granulosa-cells[3] and when it was shown that theca-cell tumours exerted profound oestrogenic influences[4] it was generally accepted that theca-cells were capable of hormone-secretion. The precise character of the hormone elaborated by these cells is still debated. Although some clarification has been made there is still disagreement as to its precise nature. Some of the obstacles to a proper appreciation of the hormonal effects of the theca-cells are no doubt due to the irreconcilable viewpoints concerning the origin, action and potentialities not only of the theca-cells but also of the other constituents of the ovary, namely the granulosa- and stroma-cells. The clinical effects of theca-cell tumours or proliferations of these cells cannot be satisfactorily appreciated without recognition of the functional capabilities of each of the ovarian components.

The effect of luteinization in theca-cells is still conjectural. There is as yet no conclusive evidence by which luteinization in theca-cell tumours can be regarded as exerting different functional effects than the non-luteinized or partially luteinized variety.

Although theca-cell proliferations with luteinization have been frequently observed

and recorded in relation to the lutein cysts of chorionepithelioma and hydatidiform mole, corpus-luteum cysts. theca-lutein cysts, follicular cysts and persistent corpora lutea, correlation with coexistent uterine reactions has not been properly established. Whatever the uterine disturbances occurring simultaneously with any of these pathological states within the ovary, whether irregular cycles, haemorrhage or amenorrhoea, it was the follicle that was generally conceded to be at fault. It did not seem to matter whether the follicle contained granulosa-cells, whether the granulosa-cells were degenerating or multiplying, or whether they were luteinized. Nor did the size and the number of cysts, the extent of any alterations in their intrinsic or surrounding structure seem to influence the generally accepted notion that the follicle, *per se*, was responsible for the co-existing uterine disturbances. Why the luteinized theca-cells, the occurrence of which is common to all of these pathological states, should have been almost completely disregarded except by a few observers is reasonably apparent. Firstly, the alterations in the theca-cells of the human ovary are less obvious or are of seemingly less significance than those in the follicles to which they are usually related. Secondly, despite the clinical finding of sterility, haemorrhage or amenorrhoea, endometrial biopsy, which is a commonly adopted procedure in the diagnosis of menstrual vagaries, occasionally does not accurately reflect ovarian dysfunction when such in fact exists.

Because in the baboon ovarian dysfunction could be estimated by fluctuations of the sexual skin apart from menstrual disturbances[5] and because ovarian and endometrial biopsies could be obtained repeatedly if necessary at specific times in the cycle, a relation was shown to exist between extensive theca-luteinization and irregularities of the menstrual cycle. Since the essential characteristics of the ovario-uterine relation of the human and the baboon are very similar, it appeared likely that an analogous syndrome existed in the human.

In this communication, the characteristic alteration of theca-cells in the human ovary which lead to the formation of yellow plaques will be examined. The various stages in the life cycle of these reactions will be shown and a classification based upon their morphological characteristics is suggested. Evidence will be presented to show that luteinization of such theca-cells is a frequent finding in abnormal menstrual rhythm and is probably causally related to the uterine aberrations which may be encountered. Finally, an analysis of these findings will be made in an attempt to correlate these thecal reactions with the known functional aberrations of other thecal structures, namely, the theca-cell tumours.

Material.

The material which forms the basis of this study was collected during the past 8 years. The ovaries and uteri were obtained from women who had been operated upon because of excessive bleeding or other uterine evidence of endocrine disorder. Many of these patients, in the 4th and 5th decades of life, had experienced a satisfactory childbearing career. Owing to the supervention of irregular cycles and profuse bleeding they were constrained to seek medical advice. When both ovaries had been removed at operation they were cut serially and the sections stained with haemotoxylin and eosin. Sharlach R was used for occasional sections from each ovary and clear sections used for refraction study with the polarizing microscope.

Observations.

The extent of ovarian participation in the cycle of the human female is not so great as that which occurs in lower forms.

The number of human primordial follicles maturing in each cycle is much less than in ovaries of other primates. Whereas in the baboon as many as 60 follicles may mature, in the human not more than 8 or 10 ripening follicles are encountered in each cycle,[6] and whereas corpora lutea are produced in abundance in many mammals it is rare in the human, as in the baboon, for more than 1 to be produced at a time.

Since the rhythmical uterine changes in the human are much more pronounced than those in other mammals, the physiological stimuli arising out of follicular growth, corpus luteum formation and regression of these processes must be relatively more intense in the human than in other species. In other words, the achievements of many follicles by way of uterine growth, in say the baboon, is accomplished by a single follicle in the human. Any pathological variation in the cyclical activity of human endometrium must therefore be induced by relatively less apparent dysfunction in the ovary than would occur in other mammals. Realization of this fundamental characteristic of the human ovary is essential for an appreciation of how slight may be the aberration necessary to interfere with the normal rhythmic changes in the endometrium.

In normal ovaries the incidence of theca lutein cells apart from those related to corpora lutea is not easily established since the ovaries, as a rule, are removed for some gynaecological complaint. Luteinized theca-cells in ovaries obtained in this way occurred more frequently in our series than was originally anticipated, and their extent and distribution was not always reflected clinically by the severity of the menstrual disorder. Mild irregular bleeding was associated with extensive theca-cell luteinization and conversely, profuse haemorrhage occurred with only slight thecal activity. In general, the pattern of thecal proliferation in the human was the same as that which was encountered in the baboon.

The theca of ripening follicles. Around the primordial follicle, the theca is barely if at all distinguishable from the surrounding stroma. With ripening of the follicle some alteration may begin to occur, although this is not a constant feature. The cells of the theca interna may differentiate and become distinct from the theca externa while cells of the latter retain their similarity to surrounding stroma. The cells comprising the many layered theca interna may show intense activity despite the small size of the ripening follicle to which they may be related. They are usually closely packed, but may be separated by oedema; they are large, round or polyhedral, often with indistinct outlines. The cytoplasm is finely granular, pale and may contain lipoid particles. The latter are more in evidence in later stages when regression of the follicle commences or has been in progress for some time. The nuclei are ovoid or round, single or binucleate and usually eccentrically situated. Mitotic figures may be numerous (Fig. 1). Sometimes theca-cells retain these epitheloid characteristics long after follicular atresia has commenced. In addition they may luteinize and persist when evidence of the follicle to which they were related has disappeared. Shaw[7] states that proliferation and hypertrophy of theca-interna-cells continue in the atretic process and that the cells become scattered among the neighbouring stroma-cells. That they may be evident in the stroma surrounding corpora albicantia is confirmed by our own observations. Luteinization of theca-cells is independent of granulosa-cell luteinization since it may occur not only when the granulosa-cells do not luteinize but also in the complete absence of the latter. Since these alterations in theca and granulosa may occur only in isolated areas

of a follicle they may not be observed except in serial studies.

The process of follicle ripening is not invariably accompanied by differentiation of the theca. A large number of follicles ripen, attain maximal size, regress and disappear without any visible alteration of the surrounding theca-cells. Why some maturing follicles should not show any visible thecal differentiation whereas others have an extremely active and well differentiated theca has not been determined.

The theca of atretic follicles. Theca-cells are most constantly observed at the periphery of corpora lutea. At this somewhat advanced stage of their life cycle they, like the granulosca-cells, are also luteinized and form the para-lutein-cells of the corpus luteum. The characteristics of the luteinization observed in these cells are but rarely seen around cystic or atretic follicles. When theca-cells around cystic follicles do present the typical features of para-lutein-cells there is frequently also some luteinization of the granulosa-cells. This type of cyst is observed in the presence of chorionepitheliomata and hydatidiform moles, and is known as a theca-lutein, paralutein or lutein cyst. Such a cyst may be indistinguishable from cysts of the corpus luteum. Cysts of the corpus luteum are usually recognized by their large central cavity, the central coagulum, the presence of a lutein layer of granulosa-cells, and by the clinical evidence of prolonged progestational activity. These criteria for cysts of the corpus luteum are not sufficiently adequate to differentiate such structures from a follicle which has failed to rupture and in which luteinization of theca and granulosa particularly has occurred. It is therefore possible that many structures considered to be cysts of the corpus luteum are theca-lutein cysts in which luteinization of granulosa is extensive although not as great as that occurring in the theca-cells.

Active proliferation and luteinization of theca-cells may occur, as has been indicated, without luteinization of the granulosa. Fig. 2 shows part of the wall of a follicle in which luteinization of the theca is marked. There were numerous mitotic figures among the theca-lutein-cells (Fig. 2) indicative of pronounced theca-cell activity. The intense capillary permeation and intercellular haemorrhage exceeded normal intensity. The granulosa-cells were also increased in number and contained many mitotic figures but did not show characteristic features of luteinization as normally encountered in corpora lutea. Such a structure may be devoid of granulosa-cells in which case it may be regarded as a theca-lutein or paralutein cyst. Between the two extremes one, where the granulosa occurs throughout the cavity and the other, where no such cells are found, wide variations in the ratio between theca- and granulosa-cells may be encountered. In either of the granulosa or theca layers luteinization may occur in all or part of the cells present.

Luteinization of theca-cells around atretic follicles has been observed in ovaries with a co-existing corpus luteum and is of regular occurrence in early pregnancy. The process may also be extensive in the presence of persistent corpora lutea. Such a relation during the menstrual cycle is, however, rather infrequent and of limited extent. The involvement of large numbers of theca-cells, visible macroscopically as yellow plaques, henceforth termed corpora thecale lutea, was not observed in conjunction with corpora lutea in this series.

In addition to the finding of varying proportions in the numbers and degree of luteinized cells, differences in the character of the luteinization may also be observed. In Fig. 3 the thecal reaction is less frequently encountered than those so far described, but it illustrates a variation in the lutein change which may occasionally be ob-

served. These cells surround an atretic follicle in which the granulosa-cells have completely disappeared and into which there has been extensive haemorrhage. The large number of vessels with thick muscular walls permeating the theca form a useful criterion for the identification of the thecal nature of this structure since such vessels never permeate granulosa-cells. In corpora lutea they extend between lobules of granulosa-cells but not among the cells themselves. An intense vascular response with capillary haemorrhage into the interstices of theca-cells is a familiar and frequently associated finding in diffuse theca luteinization. A high power study of this section (Fig. 3a) reveals the lutein-like nature of the reaction. This is not apparent in studies with low magnification, and is therefore unlike corpora lutea in this respect. High magnification reveals a large clump of cells which are strikingly similar to the luteinized theca-cells shown in Fig. 2. In some specimens the relation is only demonstrable in studies with oil-immersion. It is this type of lutein reaction, limited in extent in this specimen, which we have encountered in the yellow plaques at the periphery of atretic follicles. The ovary from which this section was obtained contained several such areas of theca-cells unrelated to each other.

Figs. 4 and 4a illustrate cytoplasmic changes in theca-cells around an old atretic follicle, identical with those which occur in corpora lutea. Here, however, the nuclei have retained their original stromal features and, in many instances, have undergone little change. The demarcation between cell forms is not abrupt.

The lutein theca-cells so far described occur around follicles in which the general form of the follicle is retained. The lining of such a follicle may be that of endothelium or degenerating and flattened, not easily identifiable, granulosa-cells. The atretic follicle is usually regarded as having a layer of centrifugally proliferating theca-cells separated from the cavity lining by a layer of hyaline. The atretic follicle may not always be apparent despite thecal proliferation and luteinization. The fluid from its cavity is absorbed or perhaps is replaced by connective tissue and hyaline deposition (Figs. 5 and 5a). In such instances one finds a solid mass of theca-cells without a central cavity and the peripheral part of the mass is continuous with the surrounding parenchyma. There is no evidence of encapsulation, and medium-sized blood vessels pass from unaltered theca through the luteinized theca-cells without interruption. Although the cells of the corpus thecale luteum merge with the cells of the stroma there is frequently a distinct demarcation between the two. The corpus thecale luteum may contain undifferentiated theca-cells identical with those of the surrounding stroma.

The most frequently observed response in theca-cells within the ovaries from women with manifestations of gynaecological endocrine disorders is represented in Figs. 5a and 6a as well as in Fig. 7a. These cells do not resemble the lutein-cells previously described. They contain a more finely granular cytoplasm. The nuclei are neither as large nor as pale. Frequently the similarity is so slight that any relation between the 2 types appears remote. However, when these theca-cells are compared with the para-lutein-cells of an approximately 30-day-old corpus luteum there is no doubt as to their similarity. Figs. 7 and 9 show such corpora lutea and the detailed structure of their theca-cells. When the latter are compared with those of the corpora thecale lutea in Figs. 5a, 6a, 7a (high power sections of Figs. 5, 6 and 7 respectively), the pale, finely granular cytoplasm and deeply stained nuclei are readily discernible. The fat content of such cells is

high and is represented in haematoxylin and eosin stained sections by clear spaces. Their similarity to the cells of the adrenal cortex is remarkable and is probably not without significance. The gross appearance of masses of these cells is that of pale or deep yellow plaques variable in size, some no larger than a pin head. There may be one or several in number and they may be scattered throughout the ovary. The point at which they may be regarded as theca-lutein-cell tumours is debatable. Since these masses of theca-cells are able to revert to their stromal form whereas theca-cell tumour growth appears to be an irreversible process, this feature of reversibility, on the one hand, and irreversibility, on the other, would seem at present to be a distinguishing characteristic between the 2 conditions. From the foregoing it is apparent that theca-cell proliferations with or without luteinization may occur with any of the recognized forms of follicular degenerations.

Because of their relation to various types of atresia, the following classification for theca-cell proliferations is suggested on the basis of a nomenclature applied to the Graafian follicle by Aschoff.

I. *Corpus thecale luteum.*

(*a*) Without granulosa-cells or with degenerating granulosa-cells. (These give rise to para-lutein or theca-lutein cysts).

(*b*) With luteinized granulosa-cells. (These produce lutein cysts usually associated with chorionepithelioma and may be confused with persistent corpora lutea).

II. *Corpus thecale luteum fibrosum.*

III. *Corpus thecale luteum candicans.*

IV. *Corpus thecale luteum hyalinum.*

V. *Corpus thecale luteum restiforme.*

In Group I the original form of the follicle is retained, the granulosa-cells may be degenerating; the theca may, in part, retain stromal features and hyaline deposition may have occurred between the theca and basement layer of granulosa cells or their remains. (Luteinization of granulosa-cells in cystic or atretic follicles without any coincident change in theca-cells gives rise to a granulosa lutein cyst. Though probably related to the structures enumerated above, it is not considered in this classification of thecal reactions.)

In Group II granulosa cells are not present, absorption of liquor folliculi has taken place, the cavity is filled with a few connective tissue cells and a hyaline ring may be found around these cells. External to this ring are found the luteinized theca-cells.

Group III represents lutein reactions occurring around a collapsed corpus atreticum in which the hyaline laminae of opposite sides, when they exist, become opposed with obliteration of the central cavity.

In Group IV there is a lutein reaction surrounding follicles in which collapse has not occurred, but hyaline tissue invades the cavity with a few nucleated connective tissue cells.

Group V indicates a lutein reaction around primordial or small maturing follicles. These were not observed, but are theoretically possible.

It must be appreciated that in proliferation and luteinization of theca interna during follicle degeneration, the extent of the thecal process is variable. It may be very slight or it may permeate extensively in an eccentric or centripetal manner through the stroma and so give rise to the various patterns which are observed in these states. Furthermore, the classification does not take into consideration quantitative values of activity which may be of paramount significance in attempting to assess the

endocrine effects of these reactions upon the uterus.

It has thus been shown that the theca-cells surrounding a maturing follicle may behave in one of several ways. They may not undergo any change whatsoever regardless of whether the follicle attains full size before becoming atretic. Sometimes intercellular oedema and pervasion of the theca interna by blood capillaries and lymphatics are the only visible alterations which have occurred before atresia commences. Variations of the atretic process may have their beginnings in the first part of the cycle for that is when the atretic process is first evident even in normal cycles. When the normal sequence of events which usually result in ovulation and corpus luteum formation is disturbed, atresia and corpus thecale luteum formation is one of the expressions of such dysrhythmia which eventually leads to menstrual anomalies. The alteration in the character of the theca-cells whereby they assume epitheloid features, acquire fat and take on the peculiarities of lutein-cells and lay down hyaline tissues, may have its physiological culmination in the formation of yellow masses, the cells of which resemble paralutein-cells approximately 30 days old. The alterations in the theca may proceed and its fat content increase. Finally they may revert to their original or stromal character with complete loss of thecal identity.

The follicle around which thecal activity is observed may be atretic and collapsed, there may be extensive haemorrhage into or around its cavity, its granulosa-cells may be completely or partially destroyed and the latter may be luteinized to greater or lesser degree. The theca-cells may extend into the stroma of the ovary in an eccentric fashion and may form a mass of considerable size comparable in extent to that of a corpus luteum. Such a structure is here termed a corpus thecale luteum.

The frequency with which these formations of theca cells are encountered in association with some menstrual anomaly suggests that the disturbances in menstruation are occurring as a result of the corpus thecale luteum. However, the theca-cells, like the uterine aberration, may be merely an expression of the same endocrine dysfunction. Causal relation may not exist.

Although the endometrial pattern in the presence of theca-cell luteinization does not concern us at this stage it may not be amiss to indicate some of the observations which were made in this respect. The diversity in the pattern of theca-cell reactions may be associated with corresponding varieties of endometrium but a lack of material forestalls at present any statistical analysis of such a relation. A wide range in the uterine reactions and clinical disturbances is nevertheless observed in the material so far studied. Fig. 10 illustrates the endometrium which occurred with the theca-cells represented in Figs. 6 and 6a. According to the classification they are of type I(*a*).

This patient, Mrs. T., age 50, had prolonged bleeding with excessive menstrual loss and irregular cycles for 2 years preceding operation. The duration of menses was usually 2–3 weeks during this time. The endometrium showed cystic dilatation of some of the glands of the same specimen.

Mrs. H. A., age 48. (Microphotographs are not represented since the thecal reactions were not strikingly different from those of the previous case.) This patient supposedly reached the menopause at the age of 40, 8 years prior to admission. Three months previously she commenced bleeding and continued with moderately heavy loss until operation.

The uterus contained a thick polypoid endometrium and there was luteinization of the theca interna around several follicles. Intense haemorrhage was noted around several follicles in the same ovary, but this may have been due to operative trauma.

Fig. 11 is from endometrium observed in a case to which the thecal reaction, the most

extensive yet encountered, was of Type III. In this endometrium there is complete inhibition of gland formation in all layers, only the superficial epithelium retaining any semblance of normalcy. The reaction here is suggestive of androgenic inhibition.

Mrs. V., age 34, para 2, from whom this endometrium was obtained, had bled excessively with each period over the past 2 years. Her menses usually lasted 2–3 weeks. Previous cycles had been normal. Four transfusions, each of 500 c.cm. of blood, were required prior to operation.

Occasionally normal endometria were observed despite the presence of luteinized theca-cells and abnormal menstrual symptoms. In one of the patients under observation, the theca-cell reaction was of Type III (Fig. 7). The endometrium in this instance was very thick, soft and spongy, like that of an early pregnancy. The history was as follows:

Mrs. K., age 36, para 2, was admitted because of irregular menses, menorrhagia and metrorrhagia. Menses originally occurring at 28 day intervals now varied between 25 and 30 days. Frequently they were accompanied by flooding and clots and persisted for 7–8 days. A currettage was performed on first admission and bleeding subsided during her stay in hospital but, at the next cycle, brisk uterine haemorrhage ensued and operation was then performed.

Mrs. H., age 34, para 3, youngest aged 5. Fig. 3 (Type I(a)). She had no abnormal or irregular bleeding, but there was profuse pre-menstrual discharge and low mid-line abdominal pain during the week preceding the onset of bleeding. These symptoms were of 2 years duration.

The utilization of a classification for these thecal proliferations may eventually yield more information on utero-ovarian relation. So far, however, the limited available material has not afforded any reasonable correlation between the menstrual disturbances, the endometrial pattern and the extent or nature of the peri-follicular reactions, except that such exist.

Discussion.

(a) *Terminology.*

The origin of lutein theca-cells from the theca interna of atretic follicles was first recognized by Limon in 1903[8]. These cells had previously been observed in the ovaries of cats and dogs by Pflugger, but their precise nature was conjectural until the present century. Schroen in 1863, regarded them as fragments of disintegrating corpus luteum, Schulin[9] described them as epithelial structures and Harz in 1883 believed that they were offshoots of glomeruli of the kidney. The formations of theca-cells vary in different species so that it is difficult to draw conclusions as to their function in the human based upon observations in other species. The term 'interstitial cell' was applied by the earlier workers to the cells which were derived from the theca interna. Separation of these cells from the theca externa in the ovary of the rabbit leads to the formation of gland-like masses and to these masses in this animal was first applied the term 'interstitial gland'.[10] On morphological evidence alone an endocrine action was attributed to the interstitial cells by the workers prior to the discovery and isolation of the ovarian hormones. It had been recognized that in some species these cells increased at the time of sexual maturity and then diminished with age. Furthermore, a reciprocal relation with the corpus luteum was also apparent, since the interstitial glands of some species decreased with the first appearance of the corpus luteum.[11]

With the passing decades and the advent of the recent knowledge regarding hormones, less attention was directed to the histological study of these interesting cells. Shaw's histological studies in 1925[6] provided a fertile oasis of slowly accumulating knowledge concerning the nature and action of these cells in the human. Recently, there has been a renewed interest in their

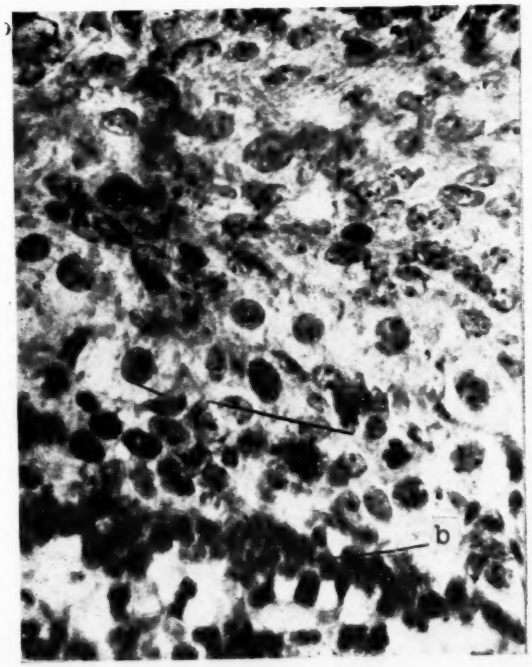

FIG. 1.

(a) Theca interna of a normal ripening follicle showing enlargement of the nuclei and occasional mitotic figures.
(b) Granulosa-cells lining wall of the follicle.

A.C.

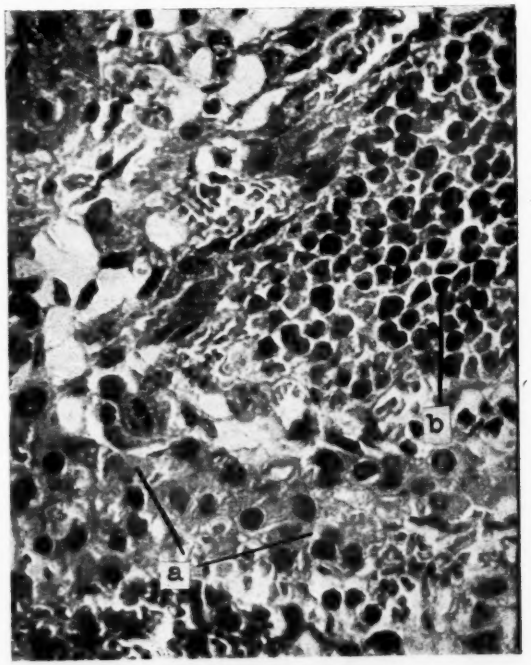

FIG. 2.

(a) Luteinized theca-cells. Note mitosis.
(b) Granulosa-cells without luteinization and with mitosis.

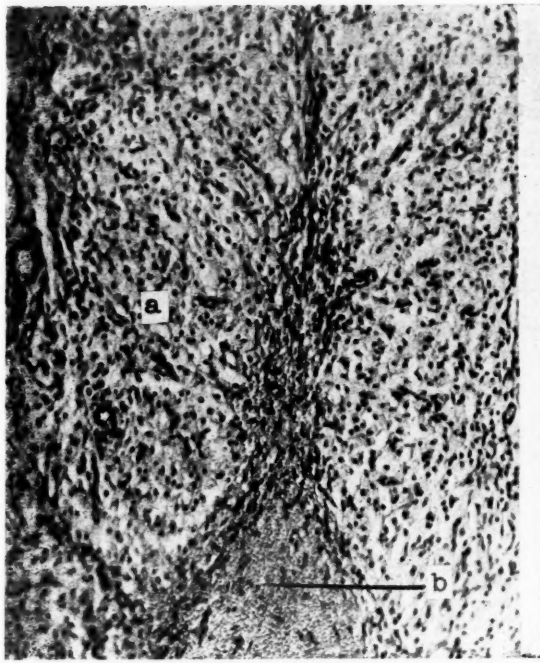

FIG. 3 (× 80).

Lutein changes in the theca around a haemorrhagic follicle devoid of granulosa-cells.

(a) Theca cells.

(b) Cavity of follicle filled with blood and few connective tissue fibres.

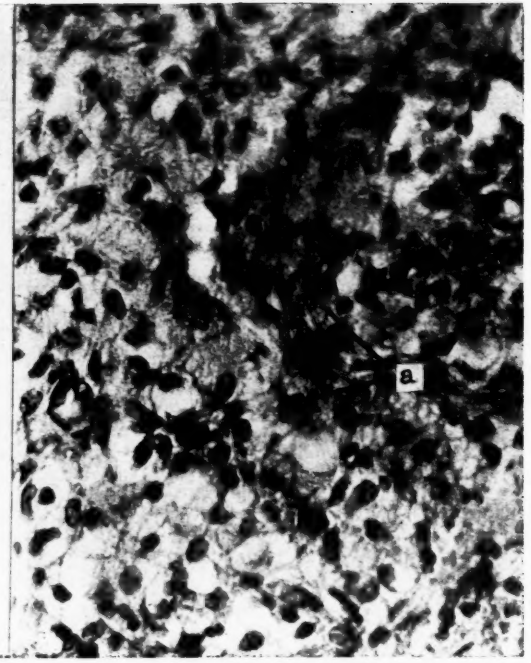

FIG. 3a (× 520).

High power of Fig. 3 showing clumps of theca lutein cells (a).

FIG. 4 (× 80).

(a) Showing theca-cells with cytoplasmic changes characteristic of luteinization but without very marked nuclear alterations. Phagocytic brown staining cells were very numerous in the cavity of this follicle.

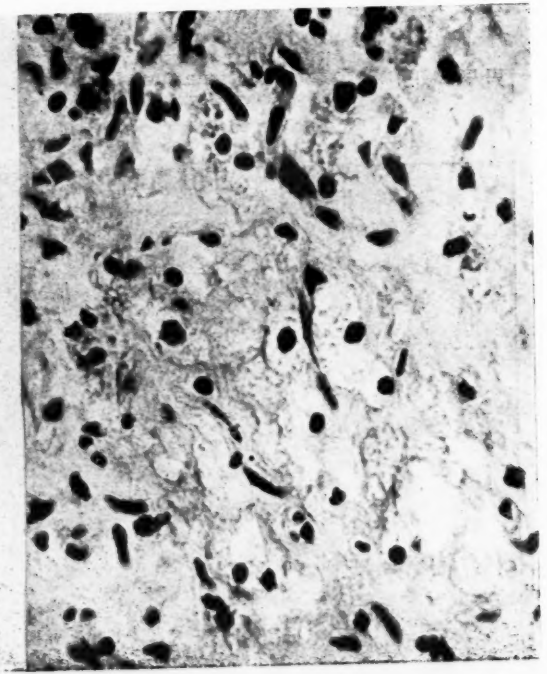

FIG. 4a (× 520).
High power of Fig. 4.

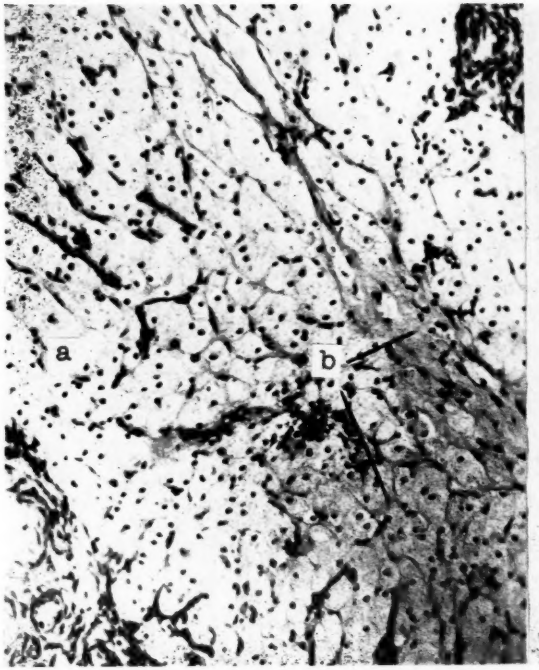

FIG. 5 (× 80).

Luteinization of theca around a follicle, the cavity of which has been replaced by hyaline tissue.
(a) Theca lutein cells.
(b) Hyaline between theca-cells.

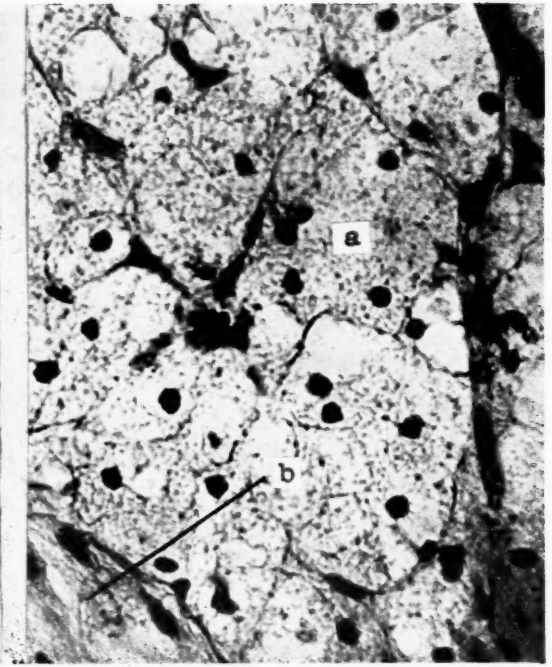

FIG. 5a (× 520).

High power of Fig. 5.
(a) The typical granular changes of luteinization in the cytoplasm of theca-cells.
(b) Hyaline deposition.

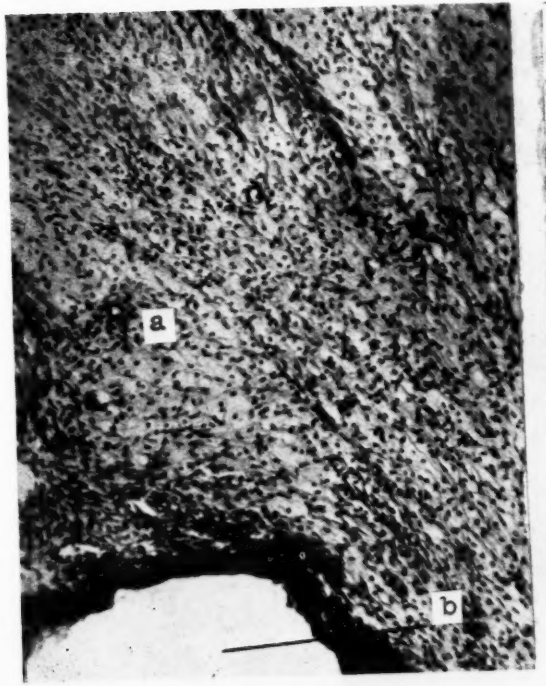

FIG. 6 (× 80).

Thecal luteinization around an atretic follicle.
(a) Lutein theca-cells.
(b) Cavity of follicle.

A.C.

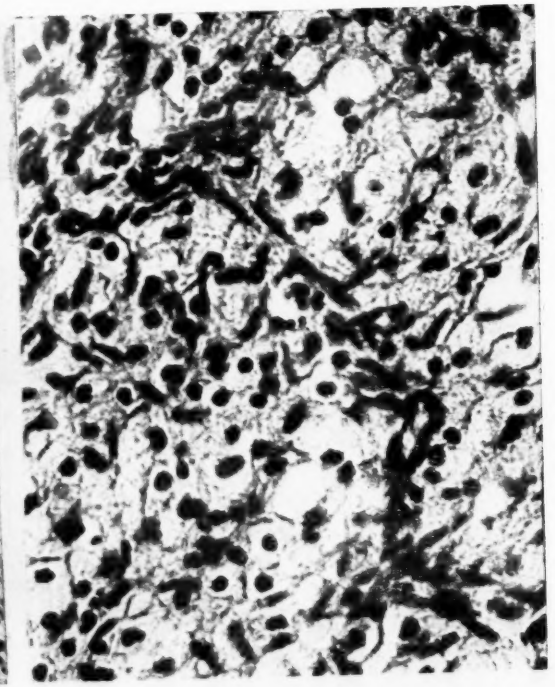

FIG. 6a (× 520).

High power of theca-cells in Fig. 6.

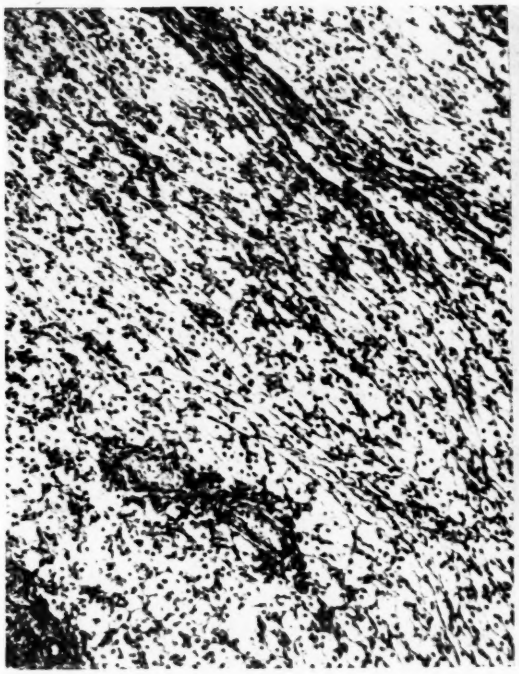

FIG. 7 (×80).

Lutein theca-cells without any evidence of a follicle. The admixture of undifferentiated and lutein theca-cells is evident in this specimen.

FIG. 7a (× 520).

High power of Fig. 7.

A.C.

FIG. 8.

Corpus luteum, approximately 30 days old.
(a) Paralutein-cells (compare with Fig. 61).
(b) Granulosa-cells.

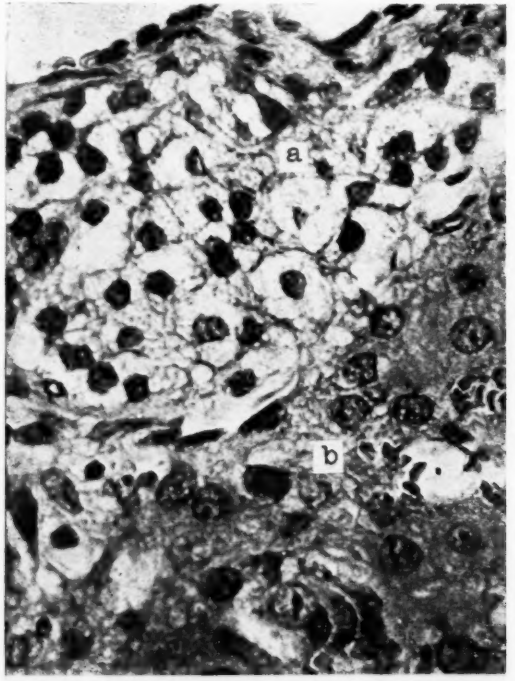

FIG. 9.

Corpus luteum, approximately 16 days.
(a) Paralutein-cells.
(b) Granulosa-cells.

FIG. 10.

Endometrium from same case as Figs. 6 and 6a, showing cystic dilatation and normal progestational glands.

A.C.

FIG. 11.

Endometrium (Case Mrs. V.) with complete inhibition of gland formation.
(a) Superficial epithelium of uterine cavity.

function in view of the potential relation of the cells to the theca-cell tumours. Shaw's work and the studies of his predecessors indicated that in the human the theca lutein cells remained confined by the external theca of the follicle, and the cells rarely were scattered through the ovary. Hence, the interstitial gland was not a usual constituent of the human ovary, apart from aggregation of thecal cells confined to the follicle. The occurrence of these cells was indicative of follicular atresia. This author, from his morphological evidence revived the plausible suggestion of a theca-cell endocrine function. Since then the controversy of whether these cells have a hormonal action, or are merely a manifestation of a degenerative process, continues to exist. It has been shown, though not conclusively, that they contain oestrogen, but whether they act as storage depots or actually produce the hormone is also conjectural. With the introduction of endocrine concepts, the problem of the function of these cells and the structures they form has assumed additional complexity.

The word ' lutein ' was originally applied to a cell which had a yellow appearance due to the presence of a pigmented fat, the nature of which was at that time unknown. By common usage, the term has been applied to the corpus luteum, both granulosa- and theca-cells. Recently, advantage has been taken of the knowledge that the lutein cells of the corpus luteum form progesterone, to label as true luteinization only those tissues which function as a source of measurable amounts of progesterone. This extension of the meaning of ' lutein ' is, in our opinion, unjustified, and in this discussion further attributes than are implied in the original use of the term will now be considered. Any cell within the ovary, whether granulosa or theca, which, because of the pigmented fat it contains, produces a yellow colour macroscopically, will be considered as a lutein cell, paralutein referring specifically to the theca-cells of a corpus luteum. One other item of descriptive terminology is of some concern. Many terms have come into use in connexion with theca-cell proliferation and luteinization. The variations in these terms are so great that the precise meaning intended by the respective authors has been lost. May the term 'interstitial gland', which was first applied to normal gland-like thecal reactions in the cat, be applied with justification to thecal reactions in the human, where they normally do not form a gland-like structure, nor do they function as a physiological unit in the cyclical phenomena of the ovary? Furthermore, it has been shown that in rodents, the interstitial gland is not derived solely from theca interna but that it is derived partly from germinal epithelium.[12] The term ' interstitial gland ', therefore, seems inappropriate for the human and only further studies upon the comparative physiology of these cells can unfold the obscurities of the problem. Consequently, the use of the terms, interstitial cells, interstitial gland, interstitial mass and interstitial body will be discontinued in this discussion where it refers to human theca-cell reactions. On the other hand, the retention of the term theca tends to correlate the benign reactions of these cells with the activity encountered in thecomas and lutein theca-cell tumours to which they are undoubtedly related. Despite the rejection of terminology which is applied to thecal reactions in lower forms their similarities are not disregarded. There seems little doubt that the thecal proliferations in human and other forms arise as a direct or indirect result of pituitary (ICSH) stimulation.[13] The fact that they occur in the human as a regular event, not only during the early part of pregnancy when placental gonadotrophes exist in large quantities, but also during the normal or aberrant menstrual

cycle, supports the contention that a pituitary factor is responsible for these changes.

(b) *Developmental Considerations.*

The theoretical determination of the endocrine function of any group of cells sometimes entails embryological considerations. Much of the controversy regarding the endocrinal function of theca-cells revolves, unimportant as it may be, around the question of whether these cells, derived from mesenchyme, can produce the same hormone as the granulosa-cells which are derived, according to some, from coelomic epithelium. Because they are morphologically the same as the interstitial cells of Leydig in the testis, it has been suggested that they are the site of ovarian androgens,[14, 15] again an assumption based upon embryological data, subsequently supported by experimental evidence. Much of the confusion regarding the hormonal *rôle* of these cells is based upon the present unsatisfactory knowledge concerning the development of these cells. Because there is still conflicting information regarding the nature of the secretions produced by the individual components of the ovary and concerning the capacity of these elements to alter the character of the particular hormones they produce, many of the hypotheses in regard to the origin of these hormones have been based upon embryological assumptions, themselves not in complete accord.

Elaboration upon this aspect of thecal activity is not the purpose of this paper, but one consideration regarding the embryological theca-granulosa relation is of some significance in understanding the reactions of theca-cells in the adult ovary. The most recent work[16] concerning the embryology of the human ovary disclaims a unified origin of theca- and granulosa-cells, and attributes the origin of granulosa-cells to coelomic epithelium. The dependence of the oogonium, which has an independent origin to that of either theca- or granulosa-cells, upon the symbiotic and correlated activities of these latter structures throughout their life cycles is established. The fate of the ovum is shown to be dependent upon the synergistic action of theca- and granulosa-cells. This synergism is maintained throughout the life of these cells. It is, therefore, not surprising that the multiple variety of thecal reactions observed in the adult are invariably related to the function of the follicle. The histological similarity between theca-cells and granulosa-cells in their many activities within the ovary such as occurs in corpora lutea, in corpus luteum cysts and in lutein cysts and corpora aberrentia[17] is a time-honoured one in the life cycle of these cells, for in the primitive ovary the granulosa-cells which encircle the oogonium are at one stage indistinguishable from the theca-cell primordium which surrounds them.

The fate of these structures seems to be determinedly interwoven from the time of their inception in the foetal ovary to the senescent phase of their existence. It is logical that all cell-structures within the ovary act harmoniously and function as a correlated mechanism. Alteration in the function of the follicles may conceivably alter the reactions in the theca, although destruction of the former does not necessarily prevent further proliferation of luteinization of the theca.[18] Because of this mutual affinity, the cells of the theca interna are capable of reacting in the manner which has already been described, that is, by proliferation and hypertrophy with resulting epitheloid features. When atresia occurs, these cells may luteinize before reverting to their original form, a faculty of which granulosa cells are incapable. Since the theca is not specific for any given follicle and may become related to a new follicle

merely by displacement and rotation of the follicle during the ordinary course of maturation, such a theca retains its capacity to proliferate in a new sphere of follicular influence. Therefore, the theca of a given follicle may have been related, or come to be related, to any other follicle within the same ovary and it has a capacity for differentiation, proliferation and dedifferentiation greater than that of any other tissue within the ovary.

(c) *Formation of Corpora Thecale Lutea.*

In the aberrant processes of thecal proliferation which are observed long after any evidence of the originally related follicle, it is apparent that the extent of thecal change in many instances, exceeds the limit of what is commonly regarded as theca interna. Since theca interna and theca externa both arise from mesenchyme it is conceivable that the latter may respond in given circumstances to the same stimuli as does the theca interna. It would seem that the specific reactions which are commonly observed in theca interna occur because of a spatial relation to the granulosa-cells or the ovum of the follicle. Furthermore, that under the conditions which lead to the formation of corpora thecale lutea, where extensive areas of the ovary have been involved, the development potentialities of the theca externa have been evoked, and consequently it is capable of luteinization in the same way as does the theca interna. The theca, therefore, not only maintains its capacity to proliferate, but it is capable of calling upon its reserve in the surrounding parenchyma when the occasion demands.

The dynamic character of theca-cells is indicated not only by their capacity for change, but also by the presence of mitoses even in their lutein form. Mitoses in granulosa-lutein-cells, on the other hand, have not occurred in our experience. Once a corpus luteum is produced, the granulosa-cells form a very stable structure with little, if any, capacity for continued growth. That lutein changes may occur in the theca of a follicle before ovulation has occurred with remnants of the ovum *in situ*, suggests[19] that aberration of the menstrual cycle, in so far as it may be due to thecal activity, may have its beginnings in the first part of the cycle. The second part of the cycle, dominated by the corpus luteum, may reasonably be expected to be less subject to disturbances than the first part when atresia is first apparent. The contention has been made[20] and investigations in this laboratory support this view, namely, that disturbances in the menstrual rhythm are essentially the result of aberrations in the follicular or first phase of the cycle, and that the corpus luteum phase is the most precise in the duration and the stability of its activity.

The various forms of thecal reactions which have previously been classified, obviously have different potentialities according to the ratio of luteinized and non-luteinized theca and granulosa-cells The precise nature of their specific activities is not yet fully apparent in view of the limited extent of available material upon which such a study must be based. Certain characteristics have, however, become obvious as has already been shown.

(d) *Clinical Considerations.*

In the presence of the corpus luteum of menstruation, the proliferation of theca cells is not invariably as great as that which occurs in its absence. A similar relation as previously noted, has been observed in other species where the normally occurring interstitial body begins to disappear when the corpus luteum first forms. Some of the normal progestational endometria which were observed in conjunction with microscopical thecal proliferations may have been

due to the influence of a co-existing corpus luteum. In one case under observation the endometrium (of ovary, Fig. 7) simulated an early pregnancy reaction, but without villi, and was extremely hyperplastic. Goodall[21] refers to a uterus which possessed all the characteristics of a 3 months pregnancy, except that neither a pregnancy nor a corpus luteum was present in either ovary. One ovary contained follicular cysts, the largest of which had "a thin sickle of internal capsule lutein-cells covering the circumference of the sclerosed cyst wall." The phenomena of bleeding and amenorrhoea in luteinization of the ovary may perhaps further be illustrated by reference firstly, to a patient observed by Dougal[22] with a history of 9 months' irregular haemorrhage followed by $5\frac{1}{2}$ months' amenorrhoea, preceding operation for a primary chorionepithelioma of an ovary. The uninvolved ovary, 4 times normal size, contained numerous cysts which microscopically were composed of lutein tissue, and scattered about the ovary were numerous islands of lutein cells; secondly, to a study by Robinson[23] of several patients, ranging in age from 15–32, in whom luteinization of theca interna occurred. In 3 cases the complaint was menorrhagia, in 1 sterility and irregular cycles, and in 2, amenorrhoea of 4 and 12 months' duration respectively. All, according to the author, were cured by resection of that part of the ovary containing the luteinized patches. The luteinization of theca-cells may, like a corpus luteum, inhabit follicle rupture,[24, 25] so that resection of these cells, while not directed at the prime agent of the disturbance may, like other more empirical methods, restore normal cycles as occurred in these particular instances. In comparing our own series with that of Robinson, the similarity in the symptomatology is obvious, despite the fact that the age groups are dissimilar. Sterility was not a feature of the older group, some having had as many as 7 children, in an adequate reproductive life. It is quite possible that the ability of theca-cells to luteinize, produce uterine upsets and revert to its stromal form, may be sufficient to produce a temporary sterility as observed in some instances. In the words of Goodall, "One is apt to assume that any disease that has overstepped the bounds of normal restraint and of normal demarcation must then, *ipso facto*, run the whole gamut of pathological destruction. Nothing could be further from the truth."

The endocrine nature of the theca-cells has been discussed elsewhere,[1] but there are several clinical phenomena, the explanation of which has been difficult, and which in the light of what has been said concerning these cells may have a tentative solution.

The greatest incidence of menstrual irregularities and haemorrhage occurs at puberty and at the menopause. It is generally assumed that these irregularities are due to a failure of the follicular processes to lead to ovulation. The endometria in many of these cases show at least some progestational response. Such endometria are certainly compatible with theca lutein proliferations around atretic follicles in the absence of corpora lutea. One need only consider the influence of small doses of thyroid in many sterilities to appreciate how delicate is the endocrine balance necessary for the maintenance of proper function.

(e) *Relation to Tumours.*

The virilizing effect of certain lipoid-cell tumours of the ovary, theca-cell tumours and lutein thecomas, is not without its counterpart in the follicular theca-cell proliferations.[26, 27] These latter reactions are prominent at the *menàrche*[11] and menopause.[28] There is increased androgen excretion not only during the progestational phase of the cycle[29] but there is a rise, tem-

porary in nature, during the menopause.[30] According to Hamblen there may also be a reduction in the androgen output following oöphorectomy in young women. These androgen variations, relative to ovarian function, and the hirsutes of the menopause may indicate the virilizing effects of theca-cells during the periods of ovarian activity when they are in evidence. Shaw suggests that secondary sex characteristics are determined by theca-cells.

Not only are the similarities between the corpora thecale lutea and theca-cell tumours clinical in their nature, but they are most in evidence in histological examinations. Firstly, when the tumours undergo luteinization they do so in the same manner as the Graafian follicle[31]; they may be composed of large epithelioid fat containing cells similar to those described around atretic follicles, and they are invariably characterized as being separated by masses of hyalinized connective tissue plaques.[32] This latter feature which is often emphasized as characteristic of the tumours is merely an exaggeration of a process which is of common occurrence in normal ovaries. The "glass membrane" described in all the older textbooks is nothing more than hyaline deposition which occurs during normal follicular atresia.

The oestrogenic manifestations which sometimes occur in theca-cell tumours are associated with the presence of doubly refractile fat and, according to Geist,[32] when the fat is scant oestrogenic manifestations are absent. The visible fat in theca-cell tumours is, in part, a cholesterol or cholesterol ester and is limited almost entirely to the cellular elements comprising the tumour. In the connective tissue it is found only in tiny scatttered globules. The distribution of fat in corpora thecale lutea is of a similar nature. As to its character, our observations reveal that it is doubly refractile and therefore of the type which, according to Geist, exerts an endocrine actions.

It is thus apparent that the histological features of the cellular components of some theca-cell tumours are in no way radically different from the exaggerated theca-cell proliferations observed in follicle atresia. The clinical characteristics of the tumour formations may be merely the exaggeration of the reactions which apparently occur with the modified and limited theca-cell reactions around atretic follicles and therefore they do not differ radically in this respect from the tumours of other endocrine glands.

Summary and Conclusions.

1. Theca-cell proliferation may occur as part of the maturation process in the Graafian follicle.

2. Theca-cell luteinization around atretic follicles may be without clinical significance in ovulatory cycles, but are nevertheless a part of the normal atretic process.

3. Luteinized theca-cells exert an endocrine influence, the precise nature of which is as yet undetermined.

4. The formation of extensive areas of lutein theca-cells may be visible macroscopically and appear as pale yellow masses or plaques usually associated with atretic or cystic follicles which, however, may not be readily apparent.

5. Luteinization of theca-cells may be localized to small areas and, consequently, serial sections of ovaries may be necessary to determine the presence of luteinized theca-cells.

6. In the presence of extensive thecal luteinization associated with follicular atresia, disturbances of menstrual rhythm and bleeding may ensue.

7. The term "corpus thecale luteum" has been suggested for the thecal proliferations occurring in association with follicular

atresia, and a classification for the types of these reactions has been proposed.

8. The character of the uterine reactions associated with theca-cells is such that neither oestrogenic nor progestogenic influences can be attributed to them. Their activity suggests the formation of a third ovarian hormone which may exert androgenic activity, or of a modified secretion of the known varieties which is capable of distorting the balance between simultaneously acting steroid hormones of the menstrual cycle.

9. The relation of these structures to theca-cell tumours has been briefly reviewed.

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Blood-pressure of Relatives of Patients with Toxaemia of Late Pregnancy

(A Preliminary Note)

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A RISE of blood-pressure is one of the cardinal signs of the toxaemias of late pregnancy. The object of this study is to attempt to assess what part, if any, hereditary factors play in the causation of the hypertension.

HEREDITY IN HYPERTENSIVE DISEASE.

It is well known that high blood-pressure and the diseases associated with it, such as angina pectoris, coronary thrombosis and cerebral haemorrhage may affect several members of the same family. It is regrettable that reliable statistical study of the familial incidence of high blood-pressure or its mode of inheritance, if any, is not to be found in the literature, though many records of individual families in whom several members, often in 3 or 4 generations, have been affected, are available. Additional evidence on this point has come from the studies of Hines and Brown.[1] Using the "cold pressor test" they were able to demonstrate that 75 per cent of hyperreactors gave a family history of hypertension and that the reaction to the cold pressor test follows an inherited pattern, though not every individual with a hyperreaction necessarily develops hypertension. It is doubtful, however, whether a high reaction to the cold pressor test is of any value in predicting the occurrence of toxaemia of pregnancy. Browne,[2] in a study of this test, found that a peak of 150 mm. of mercury or over in early pregnancy was a fairly good, but not invariable, indication that a patient would develop toxaemia. A high basal level was a more reliable indication. Reid and Teel[3] found the test of no value in predicting toxaemia. Thus, even if the reaction to the cold pressor test follows an hereditary pattern, this is not necessarily related to the occurrence of pregnancy toxaemia.

The present state of our knowledge of heredity in hypertensive vascular disease was summed up by Maurice Campbell[4]: "There is an obvious need for much more knowledge as regards the inheritance of arteriosclerosis, especially along 2 lines—accurate statistics as to how common such positive histories are; and detailed genealogical trees in some large families with precise notes about general build, blood-pressure, etc., and causes of death. Until these data are available our conclusions must be general ones; that a tendency to

arteriosclerosis is frequently inherited, that it sometimes affects particular organs producing several cases of, say, cerebral haemorrhage in one family, and that there is some slight evidence that the underlying diathesis is inherited as a dominant Mendelian character." These words were written in 1933, but as yet reliable statistical evidence along the lines suggested has not appeared.

Heredity in Eclampsia.

A good many reports have appeared of the occurrence of eclampsia in several members of the same family. A tendency to hypertensive disease in relatives of patients suffering from eclampsia and toxaemia of pregnancy has also been noted.

Theobald[5] described a family in which both parents died of Bright's disease. Five of their children died of cerebral haemorrhage, 1 of angina pectoris, 1 of tuberculosis, 1 surviving has a very high blood-pressure and 1 died of eclampsia, though there was some doubt in the last case regarding the nature of the disease, since the patient survived 1 month, and Theobald stated that she probably died from uraemia. In the next generation 1 grandchild died of cerebral haemorrhage, 1 of eclampsia, 1 of tuberculosis and 3 surviving had high blood-pressure. The same author[6] also found a family history of hypertension in 6, possibly 7, out of 9 patients admitted to hospital with high, or rising blood-pressure in pregnancy.

Bickenbach and Kroning[7] found that 4 out of 39 eclamptic patients had 1, 2, or more cases of eclampsia in the same family. They calculated that this is a much greater familial incidence than could be expected if it were due to chance alone.

Reports of the occurrence of eclampsia, toxaemia and hypertensive disease in members of the same family have come from many other authors including Dieckmann,[8] Malpas,[9] Nevermann,[10] Tillmann and Herrick,[11] Eastman,[12] and Plass.[13]

On the other hand, great caution must be observed in cases in which hypertensive disease occurs in relatives of patients with eclampsia and toxaemia of pregnancy. The reason for this is that hypertensive disease is so very common. Robinson and Brucer[14] showed that over 40 per cent of the adult population of the United States of America are actually or potentially hypertensive, and there is no evidence to show that this finding cannot be equally well applied to the inhabitants of Great Britain. Apart from the numerous well authenticated cases of the occurrence of hypertensive disease in several members of the same family, there is no reliable statistical evidence regarding the hereditary factors concerned; this evidence, which could only be derived from a prolonged statistical survey, is urgently needed. It is clear that if hypertension affects over 40 per cent of the adult population, the chances are considerable that several members of the same family may suffer from the disease without there necessarily being any hereditary element. It will be shown in the present study that severe hypertension was found in relatives of pregnant patients who were treated as controls and who were not suffering from toxaemia.

Clinical Material.

This investigation has been carried out since 1938 in the Obstetric Unit at University College Hospital. The object of the study was to determine what part, if any, a familial tendency to hypertension plays in the aetiology of pregnancy toxaemia. The blood-pressure was estimated in 226 blood-relatives of 129 patients who had been admitted to hospital with pregnancy toxaemia. The blood-pressure was also

estimated in 66 relatives of 47 patients who were not suffering from toxaemia but had been admitted towards the end of pregnancy for some other reason, such as antepartum haemorrhage. The estimations of blood-pressure were made when the relatives came to the hospital to visit the patients. In any case in which the blood-pressure seemed abnormally high it was retaken after a period of rest.

Several difficulties have been encountered in carrying out this investigation. Patients admitted to the hospital are drawn from a wide area in Greater London and beyond, and it is often difficult for their relatives to get to the hospital to visit them. This has been aggravated by war conditions which have led to scattering of families and transport difficulties. Insufficient records are available to allow of statistical analysis of the results, and in the majority of cases the family record is incomplete, so that pedigrees cannot be constructed to show the incidence of high blood-pressure. It is hoped to carry on the work at University College Hospital and it is also to be hoped that other workers, in districts where some of the difficulties that have been found in dealing with London patients and their relatives are not so pressing, will be stimulated to carry out research along similar lines.

Classification of Cases of Pregnancy Toxaemia.

The cases of pregnancy toxaemia in this series have been divided into groups to correspond with the classification which is in use in the Obstetric Unit at University College Hospital. A brief *résumé* of this classification will be given and further details can be found in "Antenatal and Postnatal Care" by one of us (F.J.B.).[15] Two modifications have been made for the purposes of this paper. Cases of eclampsia are considered in a separate group and cases of chronic nephritis and pregnancy have been excluded since there were insufficient numbers of cases in this group. In addition, a case of acute yellow atrophy of the liver it not available.

Toxaemias of late pregnancy are classified as follows:

1. Pre-eclamptic toxaemia and eclampsia.
2. Chronic glomerular nephritis and pregnancy (nephritic toxaemia).
3. Essential hypertension in pregnancy.
4. Acute yellow atrophy of the liver.

A patient is said to be suffering from pre-eclamptic toxaemia if a rise of blood-pressure above the normal level of 120/80 occurs after the 20th week of pregnancy. In nephritic toxaemia, pregnancy has supervened in a patient already suffering from chronic nephritis. In essential hypertension and pregnancy the blood-pressure has been found to be above the normal level of 120/80 before conception or in the first 20 weeks of pregnancy. Cases in which an abnormally high blood-pressure is recorded after the 20th week of pregnancy and in previous records of blood-pressure are not available cannot be placed in any of the groups in this classification and thus are called cases of "unclassifiable toxaemia."

The blood-pressures of relatives of patients suffering from toxaemia are classified in the 4 groups: eclampsia, pre-eclamptic toxaemia, essential hypertension and pregnancy, and unclassifiable toxaemia. These are given in Tables I to IV. Blood-pressures of relatives of patients in the control group who did not have toxaemia are given in Table V.

It must be noted that the majority of the records in cases of toxaemia refer to patients with toxaemia severe enough to warrant admission to hospital. Patients are admitted for toxaemia if the blood-pressure reaches 150/100; if there is a rise of blood-

TABLE I.

Blood-pressure of Relatives of Patients with Eclampsia.

No.	Father			Mother			Brothers			Sisters			Remarks
	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	
F 191	—	170	100	51	110	70				20	114	68	
F 531	48	128	60	48	130	70				18	142	76	
G 36	—	—	—							—	110	78	
H 89	68	160	100	60	160	76				30	136	74	
L 173	—	—	—	61	154	90				—	108	82	

TABLE II.

Blood-pressure of Relatives of Patients with Pre-eclamptic Toxaemia.

No.	Father			Mother			Brother			Sisters			Remarks
	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	
651/34				72	164	74							
779/29				68	186	110				40	110	72	
249/34										40	100	50	Recurrent toxaemia
1022/33				55	170	90							
A 775				68	248	110							
D 726				54	146	84				32	128	70	
B 565	60	120	70	61	120	90				28	100	60	Recurrent toxaemia
B1329										—	124	80	
A1287				62	130	74							Recurrent toxaemia
D 778										20	136	72	
D 935										—	120	80	
E 534							—	196	80	42	160	78	
										32	136	62	
E 377				56	140	76				—	104	56	Twins
E 381										35	136	74	Twins
										32	128	74	
E 27				66	200	110				36	150	70	Twins. Sister is a twin
E 442										45	150	84	
E 596										38	146	88	Niece 18, 150/80
E 436				56	144	66							1st preg. normal
E 830	44	150	100	43	220	120							2nd preg. toxaemic
E 770				64	150	80	31	154	72	26	138	76	
E1002				64	216	100							Recurrent toxaemia
F 243				45	134	80							
F 375										29	124	64	
F 388	61	174	95	57	175	120				24	110	75	
										23	120	65	
G 6				46	110	78				19	120	78	
G 1										25	108	80	
Z 75										34	120	68	

TABLE II (*Continued*).

No.	Father			Mother			Brother			Sisters			Remarks
	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	
G 72				56	154	90							Twins
G 575				52	138	78							
G 471				64	160	110				31	138	80	
G 148				67	184	92				18	128	78	
G 592				56	138	80							
G 634				56	138	68	19	128	60				
H 28				56	142	76							
H 91										40	136	74	
H 391				64	150	98							
E 554							46	168	92				
H 373				59	146	70							
H 484				48	158	70				26	122	78	
H 620										28	80	50	
H 782				—	132	60							
J 8				53	134	70							Aunt, 52, 150/80
H 852				57	120	80							
H 812				53	180	110							
H 826				46	140	80							
H 833				60	130	90							
J 13				68	138	85							
J 46				49	140	80							
J 235										25	130	80	
J 245	56	156	80	56	212	120	28	130	80				
							29	126	76				
J 299	67	138	78	69	170	100							Father died of stroke
C 466				72	190	112				40	120	76	Recurrent toxaemia
										37	120	78	
J 623				61	160	105							
J 676				45	185	110				23	135	75	
E 293										—	120	85	
K 6	60	130	70	50	166	90				26	122	70	
K 51				—	120	80				26	122	70	
K 85				64	180	90							
K 538										35	154	88	
K 547	55	186	110	63	146	84				17	128	80	
K 580				49	176	100				13	100	40	
K 586				58	140	92				38	130	76	
										22	126	78	
										19	120	80	
K 604				67	220	130							
K 662				—	150	100							
K 978							33	100	55	37	120	65	
L 261										38	148	92	Aunt 64, 160/82
										31	150	70	
L 333										35	110	60	
L 432				59	150	86							

TABLE III.

Blood-pressure in Relatives of Patients with Essential Hypertension in Pregnancy.

	Father			Mother			Brothers			Sisters			
		Blood-pressure			Blood-pressure			Blood-pressure			Blood-pressure		
No.	Age	S.	D.	Age	S.	D.	Age	S.	D.	Age	S.	D.	Remarks
A1359										44	118	70	Mother died of congestive
										39	138	98	heart failure, and asthma
C 426										27	124	70	
C 540				63	154	64				36	96	60	
E 487				51	186	90	28	150	90	32	138	84	Mother's sister, 51 B.P.
										23	156	76	196/126.
E 499				51	136	76							
E 873										38	132	96	
F 281				62	230	110							
F 302	51	162	62	50	224	116				31	154	90	
										30	132	64	
F 392	—	146	72	50	148	80							
F 435				61	180	90							
F 447				58	192	112							
G 308										44	190	116	
G 583				65	196	100	41	138	72	42	176	84	
										34	180	84	
										24	122	64	
H 43				74	200	84	49	140	72	44	160	80	
							42	128	68				
H 77				57	210	100				35	124	76	
H 152							24	140	100	33	150	80	
										29	130	72	
C 540										36	96	60	
J 652				58	230	110							Father's sister, 176/100
J 927	—	165	100	—	152	100							Mother's sister, 188/72
K 157				45	160	90	17	120	70	14	108	60	
K 225				58	180	96				—	190	90	
													Father has heart disease
L 6										58	158	110	Mother died of stroke
L 159				59	158	100	31	118	76	34	112	72	
										22	100	76	
L 230	54	146	90										
L 466				48	160	100	—	128	78	30	120	70	
L 503				64	150	90	29	110	70				

pressure with albuminuria; or if there is oedema. Patients with mild toxaemia which does not reach these standards are treated as out-patients.

RESULTS OF THE INVESTIGATION.

Table I gives the blood-pressure in 12 relatives of 5 patients who suffered from eclampsia—admittedly a very small number. While the fathers of 2 of the patients and the mother of 1 were definitely hypertensive, the blood-pressure in the relatives of the remaining patients was within normal limits. This shows that eclampsia does occur in patients who have no familial predisposition to hypertensive disease.

Table II gives the blood-pressures in 106 relatives of 70 patients with pre-eclamptic toxaemia. Forty-nine of the relatives are

TABLE IV.

Blood-pressure of Relatives of Patients with Unclassifiable Toxaemia.

No.	Father			Mother			Brothers			Sisters			Remarks
	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	
578/29				83	143	70							
51/29										44	164	90	
203/34				74	240	120							
E 524													Aunt, 38, 140/72.
E 737	62	160	70	63	200	100				28	132	100	Twins
										23	116	92	
E 690	66	200	100	53	168	102				28	130	64	
E 765	58	140	80										
F 307				59	180	92				35	128	68	
										33	148	74	Father ill with high B.P.
										33	164	8	Twin sisters.
										27	130	76	
F 250							31	136	74	39	160	90	
							29	176	100	36	180	98	
F 229				62	160	100							
F 195										26	136	82	
F 362	61	210	110							30	132	84	
										25	132	68	
										23	154	96	
F 411				42	178	92	19	120	160	22	132	64	
										18	122	64	
F 399													Twins, aunt, 23, 162/80
F 440				51	180	92							
F 512				55	182	82				21	116	56	
										19	140	60	
										17	112	48	
F 577										49	158	98	
F 674										—	128	68	
G 571				43	176	110							
H 41				63	152	80	34	124	72	36	136	70	
H 648				51	90	50							
J 30										37	130	80	
J 346				59	154	90				33	148	88	
J 522				63	160	80							
J 974	—	148	96	—	130	70							
K 113										—	130	80	
L 118	52	130	70	52	130	70							
L 240	70	170	90	65	150	100							

hypertensive if the standard of Robinson and Brucer[14] is accepted. Twelve of the 51 brothers and sisters are hypertensive and 37 of the 55 parents. Many of the latter, however, have blood-pressures a very little above normal and a similar incidence of hypertension is found in relatives of control patients.

Table III gives the blood-pressure of 55 relatives of 26 patients with essential hypertension and pregnancy. Here it will be noted that 16 of the 18 mothers of these patients show definite evidence of hypertension, and that in 14 the blood-pressure is markedly raised. The mother of Case A 1359 died of heart disease and asthma and the father also died of heart disease. On the other hand, 2 of the mothers of these

patients had blood-pressures within normal limits (Case C 540, aged 63, blood-pressure 154/64, and Case E 499, aged 51, blood-pressure 130/76). Of the 9 sisters of patients in this group, 4 had blood-pressures well above normal limits, as had 1 of the 5 brothers. These results seem to show that in cases of essential hypertension there is a definite hereditary element, although some of the brothers and sisters have escaped, including the sister of Case A 1359, whose blood-pressure at the age of 44 was only 118/70.

Table IV gives the blood-pressure of relatives of patients with unclassifiable toxaemia. Here the results are similar to those in Table II, with possibly a slightly greater tendency to hypertension. This may be accounted for by the supposition that some of these patients were in fact suffering from essential hypertension.

Table V gives the blood-pressure of relatives of control patients who did not have toxaemia. Here, a similar incidence of hypertension is found to that in relatives of patients with pre-eclamptic toxaemia.

Discussion.

Certain limited conclusions can be drawn from these results. It has been shown that severe pre-eclamptic toxaemia and eclamptic toxaemia and eclampsia do occur in patients in whom it has not been possible to demonstrate a familial tendency to hypertensive disease. This might be expected for other reasons, for example, it is known that eclampsia occurs mainly in first pregnancies and that subsequent pregnancies may be entirely normal. An hereditary factor would be expected to operate in every pregnancy. Also, the incidence of eclampsia is increased in twin pregnancies.

In the cases of essential hypertension and pregnancy, however, it was found that 16 out of 18 of the mothers of patients in this group were severely hypertensive and that the mother of another patient had died of cardiac disease.

On the other hand, when the relatives of patients in the control series were examined it was found that a proportion of them suffered from essential hypertension—some of them to a marked degree. A hypertensive heredity is therefore probably of little importance in the aetiology of toxaemia of pregnancy, except in patients with essential hypertension. It may, however, be of importance in predisposing a patient to permanent hypertension after a pregnancy that has been complicated by pre-eclamptic toxaemia or eclampsia. It was not possible to throw any light on this point, or to obtain any definite evidence on the question of the inheritance of hypertensive disease. The investigation is too incomplete to draw up pedigrees of the various families studied, but, if a hypertensive tendency is inherited on Mendelian lines, and if there is a "gene for high blood-pressure," it would appear that it must be inherited as a Mendelian recessive since some of the children of parents with this disease escape the taint.

Two further points will be discussed briefly. The question often arises whether pregnancy should be terminated in patients who are suffering from benign hypertension. In an earlier paper of ours[16] it was suggested that this is not necessary in the interests of the mother since it has not been proved that a permanent exacerbation of the disease results from pregnancy. In malignant hypertension the picture is very different, and patients with this grave disease should be advised not to become pregnant, or, if conception has occurred, the pregnancy should be terminated. It must be noted that many of the mothers of patients in this series had reached the age of 60 or even 70 with severe hypertension,

TABLE V.

Blood-pressure of Relatives of Patients who had no Toxaemia (Controls).

No.	Father			Mother			Brothers			Sisters			Remarks
	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	Age	Blood-pressure S.	D.	
E 587							22	122	64				
E 245				63	170	100							
E 302										26	140	88	
B 487				64	152	66							
E 118										46	136	70	
E 300										—	140	80	
E 343										—	140	80	Aunt, B.P. 124/88
E 551				—	140	80							
E 521										29	116	70	
E 440	—	176	88	—	158	84				26	118	68	
F 113										20	136	72	
F 544	49	138	62	48	138	72							
F 716							30	124	70				
G 21				51	164	84							
G 73				40	110	78							
G 29										30	120	70	
G 31				52	130	80							
G 106				53	140	90							
G 418				51	220	130				19	116	54	Father died, heart failure
G 607	50	160	70	50	140	64							
A 237				60	120	60	23	120	60				
C 868				64	160	110				31	138	80	
										18	128	78	
G 549				69	210	100				33	124	62	
G 505										33	122	68	
F 544	49	138	62	48	138	72							
G 550										33	120	70	
G 574				51	140	80							
G 531				55	118	64							
G 577				52	164	96							
G 681	—	126	80	—	118	72				—	118	68	
F 58				61	170	100							
G 580				51	140	76							
H 22				41	128	72							
H 36										28	110	56	
H 38				58	150	110							
H 47				43	120	78							
H 42				50	136	78							
H 65										42	138	60	
										40	140	78	
										38	122	64	
H 66				61	148	82							
H 122				46	170	86							
H 148										34	116	80	
H 401										30	112	70	
H 531				70	220	90							
E 29				—	86	50				—	114	66	
H 746				72	194	82				34	80	50	
J1004	61	162	104	50	158	75	28	132	88				Uncle died of high B.P.
K 158							36	130	80	38	122	70	
							32	126	72				

which might have been present, undetected, during their pregnancies and was often revealed for the first time at this examination.

The second question is whether patients with benign hypertension should be discouraged from having children on eugenic grounds. Clearly there is little in favour of this. The evidence of hereditary transmission of this disorder is, as yet, not based on any reliable statistical evidence, and in any case the severe manifestations are unlikely to occur before late middle age or even senescence.

Maurice Campbell[4] summed up the situation as follows:

"Only exceptionally when these conditions (cerebral haemorrhage, angina, etc.) have occurred frequently and at an early age are we justified in warning against parenthood. Practically our advice is limited by the fact that cardiovascular disease is likely to occur in those stocks which are desirable from other points of view, that is to say, in their freedom from more important disabilities like tuberculosis and mental disorders. If a disease does not occur before sixty or later its occurrence may be no contra-indication to parenthood, even if it were known to be inherited with certainty, especially as the vigorous and capable type in whom cardiovascular disease is likely to occur may have excelled in almost any walk of life before the age at which the malady manifests itself."

Conclusions.

1. It is well known that a tendency to high blood-pressure may be inherited though the evidence for this is based on records of individual families rather than on statistical study.

2. Many individual reports have appeared of the occurrence of eclampsia in several members of the same family. A tendency to hypertensive disease in relatives of patients suffering from eclampsia and pregnancy toxaemia has also been noted.

3. The blood-pressure has been recorded in 226 relatives of 129 patients who were admitted to hospital with pregnancy toxaemia. These patients have been divided into 4 groups: Eclampsia, pre-eclamptic toxaemia, essential hypertension and pregnancy, and unclassifiable toxaemia.

4. The blood-pressure was also estimated in 66 relatives of 47 control patients who were not suffering from toxaemia.

5. A demonstrable difference in the levels of blood-pressure has not been noted between the relatives of toxaemic and control patients, except in cases of essential hypertension and pregnancy. Here it was found that 16 among 18 mothers of the patients in this group were markedly hypertensive.

6. It is concluded that there is not any evidence that a hereditary tendency to hypertension is of any general importance in the aetiology of toxaemia of pregnancy except in cases of essential hypertension and pregnancy.

7. The implications of these findings are briefly discussed, and it is concluded that it is rarely necessary to interrupt pregnancy in a case of essential hypertension in the interests of the mother. Nor should patients with a familial history of hypertensive cardiovascular disease be discouraged from having children, except in those very rare cases in which the manifestations of the disease have occurred frequently and at an early age.

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The Prevention of Premature Labour

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INTRODUCTION.

NEVER before has the problem of a declining birth-rate attracted such attention as now. Obviously it is not enough for us to prolong the expectancy of life of the living. To survive as a nation in this competitive world we must also salvage more life at its source. Whitton[1] has recently pointed out that in Canada, in 1921, there were 75 persons over 60 years old and 240 under 10 years old, per 1,000 population. But in 1941, only 20 years later, there were fully 102 persons in the older group pyramided on a shrinking base of 182 in the juvenile group. Thus, prevention of abortion and miscarriage, and the conservation of the premature infant, once interests of the obstetrician only, now cast their medical robes like Phrygne and stand forth in the politico-economic arena. These really are matters of national life and death.

The enormous annual wastage of lives during the neonatal period, too, has recently been commented upon by many authors. Potter,[2] for instance, points out that, in spite of steadily improving obstetric practice in the United States, there has been but very slight decrease in the deaths occurring under the age of 1 day since 1937 (15.1 deaths per 1,000 live births in 1927, as compared with 13.9 per 1,000 in 1940). Admittedly, mortality within the 1st month, during the same period of years, has decreased somewhat more rapidly—from 35.5 deaths per 1,000 (1927) to 29.0 per 1,000 (1940)—but that also is still too high.

That the problem is acute is evidenced further by an aggregate of 144,692 foetal and neonatal deaths in the United States in 1941, the last year for which statistics are yet available. As Sage[3] comments, this is more than the total number of deaths among all persons in the age-group of 5 to 29 years, and constitutes fully 10.4 per cent of the total deaths from all causes. Sandifer[4] shows that in England and Wales "prematurity" caused more deaths in 1938 than "coronary disease" or "old age," about as many as were due to "tuberculosis," and about one-third as many as "cancer." Most large hospitals in the United States and Britain report that 5 to 10 per cent of all births are premature. Peckham[5] could not find any significant improvement in the prematurity figures of the Johns Hopkins Hospital in the 40 years prior to 1936. Schwartz,[6] of the Children's Bureau, U.S. Department of Labour, Washington, writes that the estimated number of premature births in the United States in 1942 was 155,000, and that 33,500 premature infants died in the 1st month of life. Marshall[7] of the Dominion Bureau of Statistics, Ottawa, mentions that in 1940 there were 12,268 premature babies born in Canada, amounting to 5 per cent of the live births. There were fully 3,340 stillbirths ascribed to prematurity, amounting to 54 per

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cent of all the stillbirths where the period of gestation was stated; 2,900 deaths in the 1st month of life were ascribed to prematurity. To put it in another way, 50 per cent of all premature babies born in Canada in 1940 were dead at birth, or died in their 1st month. But it should be pointed out that in the whole European theatre of the war, in 5 years and 8 months of fighting, Canadian losses in killed and missing amounted to 40,975 among over 1,000,000 enlistments, a mortality of 4 per cent. It is, therefore, more than 12 times as dangerous for a premature infant to be born in Canada as it was for a Canadian man to enlist in the war. And if we take 1940 as a representative year, then during the war Canada lost 35,360 premature babies, almost as many citizens as she lost by enemy action. Is prematurity a vital Canadian problem? One suspects the truth is that, if there had not been any premature children born during the war, the population in that time would not have been decreased. And we are speaking only of prematurity and ignoring spontaneous abortion and miscarriage, which kill at least as many potential citizens.

In Chicago, Bundesen and his co-workers[8] found prematurity to be the largest single cause of neonatal death in a series of 1,043 necropsies. Intracranial haemorrhage and malformations came next in order of frequency — and, of course, prematurity contributed to a fair proportion of these deaths as well.

The death-rate in infants born too soon appears to vary directly with the degree of their prematurity. Dunham[9] demonstrated that, of foetuses born weighing less than 1,000 grams (2.2 pounds), 95 per cent succumbed; of those from 1,000 to 1,500 grams (2.2 to 3.3 pounds), 72 per cent; of those from 1,501 to 2,000 grams (3.3 to 4.4 pounds), 32.5 per cent; while of those weighing from 2,000 to 2,500 grams (4.4 to 5.5 pounds), only 8.7 per cent perished. Studies made in New York City[10] and New York State[11] indicate that prematurity doubles the neonatal mortality. Still more startling is the calculation of Potter and Adair[12] that the combined neonatal mortality and stillbirth-rate of premature infants amounts to 18 times that of babies born at term. The practical relation of this problem to national survival surely becomes strikingly apparent.

In Chicago, a determined effort has been made in recent years to lower the death-rate of newborn infants. For example, in the 4 years from 1936 to 1940 the death-rate of premature babies under 15 days was reduced by 15 per cent and of all infants by 25 per cent.[13] This result is significant, of course, but when one knows the nature of the intensive measures Hess, Bundesen, and others adopted in their life-saving campaign, it can readily be seen that not much more can be hoped for by such efforts and that the solution of the problem does not lie in saving premature infants but rather in preventing premature births. A very good summary of the whole problem is given in the Report on Infant Mortality in Scotland for 1943.[13] The dietary experiments carried on at Toronto[14] and elsewhere suggest that dietary improvement decreases the actual incidence of prematurity, and this was borne out by a vitamin E study[15] published in 1942.

In 1937, it was suggested by one of us (E.V.S.[7]) that the mechanism of premature labour might be initiated by an abnormality similar to that causing spontaneous abortion and miscarriage, as might be expected on *a priori* grounds. Developmental anomalies figure unduly prominently in any series of premature births, and further substantiate the impression that the causes of abortion and prematurity may be much the same. Sandifer[4] brings out clearly the relation that has long been obvious between

the occurence of prematurity and maternal toxaemia, antepartum haemorrhage, or multiple pregnancy. Apart from the group of congenital anomalies, there remained a large group in his study where the cause of the prematurity was not found and was therefore potentially discoverable.

DATA.

We present below a tabulated series of 63 consecutive, unselected cases of threatened and actual premature labour compiled from the practice of both authors and our colleague, Dr. Mary Wong, investigated by similar criteria and identically treated. Our results are as follows:

there was a salvage in this series of 46 cases, or 73 per cent. If we add to this the 46 cases reported in the previous publication on this topic referred to above,[15] it will be seen that the salvage amounted to at least 72 per cent. This represents a considerable number of lives saved, and such figures could no doubt be greatly improved had we felt free to use as large doses of vitamin E as we desired, without regard to its cost, and had we seen some of these patients earlier in their precarious pregnancies. Some of the very small babies have survived too, and others were anomalous and beyond the power of anyone to preserve. It is obvious that a good case,

TABLE A.—*Cases terminating in normal living infants at term.*

Number of cases	Previous abortions or other abnormal terminations of pregnancy	Blood oestrogen			Average time when labour first threatened	Symptoms			Weight of infants
		Positive	Negative	Not done		Mild	Moderate	Severe	
37	9	20	1	16	32 weeks	20	4	13	7 lb. 7 oz.

TABLE B.—*Cases terminating in normal living infants 38 weeks or younger.*

Number of cases	Previous abortions or other abnormal terminations of pregnancy	Blood oestrogen			Average time when labour first threatened	Symptoms			Weight of infants (excluding twins)
		Positive	Negative	Not done		Mild	Moderate	Severe	
21	10	9	4	8	33 weeks	7	2	12	5 lb. 2 oz.

TABLE C.—*Cases terminating in stillborn infants.*

Number of cases	Previous abortions or other abnormal terminations of pregnancy	Blood oestrogen			Average time when labour first threatened	Symptoms			Weight of infants
		Positive	Negative	Not done		Mild	Moderate	Severe	
5	1	4	0	1	31 weeks	5	1	1	?

DISCUSSION.

If we define prematurity by the criterion of 5½ pounds (2,500 grams) weight and more than 28 weeks of gestational age, even better than is suggested by the above figures, can be made out for the regimen we have used in treatment.

If it be objected that not all the patients

listed here were threatening premature labour, we may select the obviously severe threats, and those first seen during labour, numbering 28 in all. Of these, 21, or 75 per cent, were preserved, an almost identical rate of salvage. If it be pointed out that there are too few induced premature labours mentioned here, and that that ununduly favours our thesis, we may reply that we control our toxaemias so well that all go to term or near it, being ambulant throughout, and that the average birthweight of our non-eclamptic late toxaemia babies is half a pound above the normal.[16] In this series, however, 4 cases were induced, 1 for very severe recurrent pyelitis and 3 for toxaemia. Even in these 4 cases the same percentage of salvage holds. It would seem, therefore, that 3 of every 4 babies threatened with premature expulsion can be preserved.

In this study it was found that a tendency to premature labour could usually be predicted by finding a blood-oestrogen excess even in early pregnancy, confirming an observation reported[17] several years ago. That it occurred in 87 per cent of the 38 cases tested, can hardly be termed accidental. It is of interest that Hall,[18] using a vaginal smear method, has recently observed that oestrogen excess precedes abortion and miscarriage. In many of our patients symptoms of threatened abortion or threatened miscarriage had previously appeared, but these had subsided promptly on instituting vitamin E therapy or increasing the dose already being given. Such management appears to have allowed many cases, otherwise precarious, to carry through to term. However, only a large daily dose—75 to 125 mg. of Alphatocopherol—can save the situation sometimes, for if too high a tide of oestrogen undermines the piers the uteroplacental bridge goes down. There must be vigorous and adequate treatment with a potent vitamin E preparation until term. Even at this late date in vitamin E therapy it is discouraging to discover that many or most physicians employ cheap and relatively impotent products masquerading as good vitamin E—to the unduly prolonged discredit of this type of treatment.

Frequently premature labour begins, almost unheralded otherwise, with rupture of the membranes. Many a patient, too, forgetting her physician's warning, reports to him several hours after the onset of pains when labour has unmistakably set in. Thus, a valuable opportunity may be lost and delivery become inevitable before preventive treatment can be undertaken. It takes almost 24 hours, unfortunately, for vitamin E to control a case.

Accordingly, we stress the importance of a routine blood-oestrogen test at the patient's first antenatal visit. We thus have a gauge of the dangers ahead, and can institute daily prophylactic therapy with vitamin E as indicated. Indeed it can do no harm, unless the woman is a true pre-eclamptic, to give vitamin E to every pregnant patient until at least the 8th month. If, in spite of this management, the patient temporarily escapes from control, larger supplementary doses may quickly be given in order to restore the normal balance.

As pregnancy progresses the enlarging placenta requires a gradually increasing amount of vitamin E to maintain its "cling" to the uterus. This adjustment of dosage is largely a matter of judgment and experience. An eye alert to detect early symptoms of trouble is essential. It may save much later anxiety and win many a battle before the first shot is fired. Accordingly, each patient is warned to report an area of uterine tenderness, or sacral backache, or spotting of blood, or loss of amniotic fluid, or a feeling of prolapse or impending menstruation. These mean that she is escaping from vitamin E control.

A study of consecutive pregnancies suggests a definite trend towards repetitive behaviour.[19] Once the "abortion sequence" of Young[20] is established, abortion, or miscarriage, or abruptio placentae, or a late toxaemia, or premature labour tend to recur in later pregnancies. Each pregnancy seems harder to carry to term than its predecessor. It should be emphasized that an unstable pregnancy does not necessarily mean a defective infant, in spite of much opinion to the contrary. Of the 109 pregnancies in this and the previous reported groups, only 5.5 per cent terminated in the delivery of malformed children, and only 1 of these 6 with a cleft palate lived for more than 3 months. Could anything argue more clearly that the remaining 92 had a claim to salvage? Some years ago the data in the literature on all threatened abortions saved by the use of vitamin E, or progesterone or both was summarized,[21] and only 3 per cent were found to have resulted in anomalous infants.

Summary.

1. A series of 63 cases of threatened premature labour is presented. Of these 73 per cent were salvaged.

2. Of the patients in this group on whom a blood-oestrogen was done, 87 per cent showed a high blood-oestrogen, even early in pregnancy.

3. The only therapy used was vitamin E, with or without temporary rest in bed.

4. The importance of using a vitamin E preparation of reliable potency, both in adequate dosage and until term, is emphasized again.

5. Of the 109 patients included in this and our previous report, there were 6 monsters delivered, only 1, with a cleft palate, surviving over 3 months. But 92 normal living children were obtained. Their preservation would seem justifiable.

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Carcinoma Corporis Uteri in 2 Sisters Aged 34 and 32 Years

BY

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IN a prior communication[1] the occurrence of carcinoma corporis uteri in each of 2 sisters, aged 34 and 32 years respectively, was described briefly. Interest and scepticism were aroused. One eminent gynaecologist wrote to me: "I, personally, am deeply convinced that this condition *never* occurs before the menopause. . . . My mind, however, is quite open to be convinced that carcinoma corporis does occasionally occur before the menopause, and I would therefore be very grateful if you would send me a complete range of your sections in order that I may endeavour to convince myself." This was done. After studying the material he replied: "I am wholly convinced that the sections show a definite carcinoma of the body of the uterus. I have to-day discussed these sections with our Professor of Pathology and he can recall only 1 other case in a woman before her menopause in his large experience." It is probable that others were equally sceptical. It is obviously important to establish the fact that corporeal carcinoma does occur, even if only occasionally, long before the menopause. Adenocarcinoma of the uterine body is an eminently curable condition if recognized sufficiently early. It is to be regretted that many subjects of malignant disease fail to seek advice until the condition is so advanced that all hope of cure is gone. But how much greater the regret if the patient seeks advice early and the condition is not recognized because the attendant doubts the possibility of its existence. It has been decided, therefore, to present the cases in more detail with microphotographs to substantiate the diagnosis.

A complete review of the literature of premenopausal corporeal carcinoma has not been attempted, but a sufficient number of cases is cited to show that it can and does occur. The importance, then, of diagnostic curettage, even in young women who have prolonged or irregular uterine bleeding, should require no emphasis. In the case of my 2 patients there is the added interest of their being sisters.

CASE HISTORIES.

Sister No. 1.

Aged 34 years; nullipara; married 10 years, during which contraception has been practised constantly. Admitted to the North Middlesex County Hospital on April 4th, 1940, for severe vaginal bleeding of 10 days' duration. There had not been preceding amenorrhoea.

Menarche aged 15 years. Until about 28 years of age the periods were regular, lasting 3 days and recurring every 4 weeks. Then the menstrual loss became more profuse, lasting 3 to 7 days, recurring every 4 weeks. For 2 years prior to admission the loss was greater still, lasting sometimes even 14 days. Coital bleeding occurred occasionally during those 2 years. There have been irregular haemorrhages recently. The patient has never experienced dysmenorrhoea or dyspareunia. For years she has had a profuse white vaginal discharge. This discharge has been like "muddy water" for about 2 years prior to admission. There has been constant backache.

At 24 years of age a right-sided ovarian cyst, weighing 24 pounds, was removed at another hospital. (This cyst had not caused any menstrual disturbance.)

On examination the general condition was good. The breasts did not show changes suggestive of pregnancy. The abdominal findings were normal except for a long paramedian scar. But for slight uterine enlargement the pelvic findings were normal. Curettage was performed. Macroscopically the curettings suggested incomplete abortion. Microscopically this condition was excluded. The possibility of malignancy was considered, but, in view of its improbability, it was decided to postpone judgment and to keep the patient under careful clinical review.

Normal menstruation continued, except that in August there was bleeding for 1 month. In November and December bleeding became irregular, and a second curettage in January 1941 showed endometrial carcinoma. Total hysterectomy with left salpingo-oöphorectomy was performed (the right ovary had been removed previously, *vide supra*) and followed by deep X-ray therapy. The patient made an uninterrupted recovery. The uterus on section showed endometrial carcinoma invading the wall. The ovary and tube did not show involvement by the growth.

The histological material of this (and of the subsequent) case has been recently submitted to Dr. I. Doniach, whose reports are incorporated in this paper.

Histology (I. Doniach).

First Curettings (April 4th, 1940). There is a gross glandular hyperplasia consisting of closely packed convoluted acini lined by more than one layer of cells. Some acini show numerous mitoses and their lumina are filled with polymorphs. The picture is strongly suggestive of adenocarcinoma.

Second Curettings (January 7th, 1941). The acini are even more closely packed, solid and made up of atypical cells. This is a definite adenocarcinoma.

Uterus (January 17th, 1941). (Figs. 1 and 2). This is a polypoid adenocarcinoma showing malignant infiltration of the endometrial stroma, but only slight infiltration of the myometrium. The glands away from the growth show the cystic dilatation seen in metropathia haemorrhagica.

Sister No. 2.

Aged 32 years; nullipara; married 9 years; no contraception. Admitted to the North Middlesex County Hospital on October 16th, 1942, because of severe vaginal bleeding for 1 week. There had not been preceding amenorrhoea. Menarche at 13 years of age. The periods have never been very regular. The menstrual flow has lasted from 6 to 10 days and recurred every 3½ to 4 weeks. Upon a number of occasions the patient has suffered from menorrhagia with increased irregularity in the length of the cycle. She has attended the gynaecological out-patient department of 2 other hospitals because of this, but curettage has not been performed. The period in September 1942 was very heavy. While coital bleeding has never occurred, dyspareunia has been present from time to time. She has never experienced any dysmenorrhoea. There has been slight vaginal discharge intermittently over a period of years.

On examination the general condition was good. The breasts did not show signs of pregnancy. Abnormality was not noted on abdominal or pelvic examination. Diagnostic curettage was performed and yielded a piece of tissue suggestive either of incomplete abortion or corporeal carcinoma. Histology proved it to be the latter. Total hysterectomy with bilateral salpingo-oöphorectomy was performed, followed by deep X-ray therapy. Convalescence was normal.

Histology (I. Doniach).

Curettings (October 19th, 1942). (Fig. 3). These consist of fragments of a moderately well differentiated columnar-celled adenocarcinoma, arranged in closely packed acini lined by multilayered atypical cells. Many show a small lumen. Others are distended with mucoid material. Mitoses are abundant. In some areas the stroma is infiltrated with polymorphs.

Uterus (October 23rd, 1942). (Fig. 4). This contains a polypoid endometrial adenocarcinoma showing malignant infiltration of the stroma and subjacent myometrium.

Both patients have been followed up regularly. They have remained well and free from any sign of recurrence. They were last seen in September 1945. On this occasion blood was taken from each sister for Rh typing. In each the blood is group O(4). Sister No. 1 is Rh positive, while Sister No. 2

FIG. 1.

Section of uterus after hysterectomy (Sister No. 1)
Microphotograph × 25.

A.W.P.

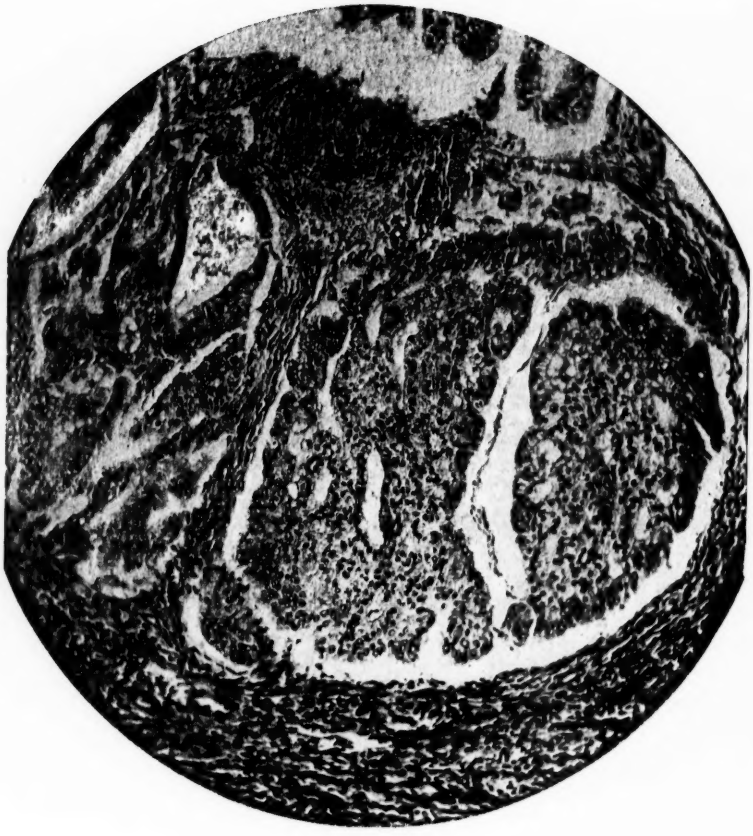

FIG. 2.

Section of uterus after hysterectomy (Sister No. 1)
Microphotograph × 100.

FIG. 3.

Section of curettings (Sister No. 2).
Microphotograph × 240.

FIG. 4.

Section of uterus after hysterectomy (Sister No. 2)
Microphotograph × 135.

is Rh-negative. In neither case did the serum contain Rh antibodies.

The patients' mother had 10 children. One sister died of meningitis at 10 months of age. The rest are alive and well. Recently another sister (Brews[2]) has undergone hysterectomy for a benign condition. The mother died of cancer of the rectum aged 68; and 2 maternal uncles died of cancer of other organs.

In view of a possible milkborne carcinogenic factor (Bittner[3]) inquiries were made into the early feeding of the 2 sisters who were my patients. From elder members of the family it was learned that they were fed artificially as "their mother never had any milk."

Discussion.

Corporeal carcinoma is typically a post-menopausal condition. In series of any size (Norris and Dunne[4]; Crile and Elias[5]; Masson and Gregg[6]) the largest number of cases occurs in the 6th decade of life. Many observers find the average age of incidence to be within the narrow limits of 56 to 58 years. While this may be so, a small but appreciable number of cases is encountered in the 4th decade (Beattie[7], 3 per cent.; Crile and Elias[5], 4 per cent.; Morrin and Max[8], 4.5 per cent.; Healy and Brown[9], 3 per cent.; Masson and Gregg[6], 3.5 per cent.; Brindley[10], 3 per cent.; Barns[11], 3.16 per cent). From time to time it is met with at the age of 19 or 20 (Smith[12]; Morrin and Max[8]; Healy and Brown[9]; Kenny[13]).

Of great interest is its occurrence in children. Hirst[14] saw a girl of 15 years of age who, 5 months previously, had had a cervical polyp removed. He excised the stump of the polyp and fulgurated the base. Eleven months later the patient returned with profuse bleeding. Another polyp was avulsed, and the uterus curetted. Histology showed corporeal adenocarcinoma. Total hysterectomy with bilateral salpingo-oöphorectomy was performed. Ten months later the patient was alive and well. Morse[15] quotes Kehrer and Neumann, who described the occurrence of corporeal uterine carcinoma in a child aged 16 months. Necrotic purulent material escaped during the extirpation of the tumour, and the child died 10 days later of peritonitis. Gilbert[16] performed fundal hysterectomy with right salpingo-oöphorectomy in a girl of 11 years of age 6 months after the onset of vaginal bleeding. The specimen showed corporeal carcinoma. In spite of deep X-ray therapy she developed extensive metastases in the chest and died 9 months after operation. Others have described uterine cancer in children but these appear to have been cervical carcinomata. Shaw[17] described a case of adenocarcinoma of the uterine cervix in a girl of 15 years, and reviewed the literature of cervical carcinoma in children and adolescents. He found 12 cases in which he considered it established that the cancer had originated in the uterine cervix. Morse[15] described a very cellular adenocarcinoma of the genital tract in a girl aged 10 years. He considered it to be cervical in origin, but states that Ewing thought it had arisen from a foetal rest in the pelvic cavity.

The other aspect of the matter is familial occurrence. In considering a familial tendency to cancer we may be interested in its occurrence in any organ of the body, but the tendency to malignant tumours in one organ in members of the same family is of particular interest. Williams[18] tells of a mother and 3 daughters who died of uterine cancer. In another family 3 sisters died of cancer of the uterus at 32, 36 and 53 years of age, as did also their mother and maternal grandmother. Auvray[19] described death from uterine cancer in a grandmother, mother and daughter. All these appear to have been due to cervical carcinomata. Kenny[20] has received information that the mother of her young

German-Jewish patient[13] has recently died, in Asiatic exile at the age of 44, of uterine cancer. She cannot ascertain whether this was corporeal or cervical, but, since suggestive symptoms, such as irregular uterine bleeding, were known to be present in 1939, the probability of corporeal cancer may be entertained.

In the Warthin family, among 174 members reaching the age of 25, 41 persons developed 43 primary carcinomas: 23 of these occurred in females, and of these 23, 15 were uterine corporeal adenocarcinomata: there was not any case of cervical carcinoma in the family (Macklin,[21] Hauser[22, 23]). Of the 15 subjects with uterine adenocarcinoma, 6 were under 45, their ages ranging from 39 to 44 years. In only 4 of these was there histological confirmation of the diagnosis. There was only 1 under 40 years of age, and in that case the diagnosis was not confirmed histologically.

Imamura[24] claims that if a predecessor with uterine carcinoma transmits the "cancerous diathesis" to her descendants, they are more liable to have the tumour in the uterus than in other organs.

While a familial tendency to carcinoma in the same organ is of speculative interest, the 2 cases described in this paper emphasize a point of great practical importance—the possible occurrence of carcinoma corporis uteri in comparatively young women.

Summary.

(1) It is erroneous to state that corporeal uterine carcinoma never occurs before the menopause.

(2) Two cases of corporeal uterine cancer occurring in sisters aged 34 and 32 years of age are recorded. The diagnosis in each case is substantiated by microphotographs.

(3) That these are not isolated cases is demonstrated by a brief review of the literature.

(4) Cases occur even in childhood.

Acknowledgements.

I should like to express my indebtedness to Dr. Herbert Rogers, until recently Pathologist to the North Middlesex County Hospital. It was he who prepared and examined all the pathological material in the first instance, and has helped me in numerous ways since. To Professor James Young of the British Postgraduate Medical School, I am indebted for his interest and to Mr. E. V. Wilmott, A.R.P.S., photographer to the British Postgraduate Medical School, for the excellent micro-photographs which he has produced for me.

Finally, I would thank Dr. I. Doniach, Senior Assistant in Morbid Anatomy, British Postgraduate Medical School, for his kindness in examining and describing these histological preparations for me. I greatly appreciate the placing at my disposal of his wide experience in the histology of malignant disease—particularly in such an instance when it is acknowledged that the subject is controversial.

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Rupture of the Rectus Abdominis Muscle During Pregnancy

BY

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IN a recent paper[1] I recorded a case of rupture of the rectus abdominis muscle during pregnancy. The rarity of this complication of pregnancy was apparent from the fact that a search through the literature discovered only 9 previous instances, my own case making the 10th. Since then 2 more examples have been recorded, by Keevil,[2] and Liggett,[3] in this country. My attention has been drawn lately to a paper by Torpin, which appeared after my case was recorded. Torpin,[4] in describing his own case, has gone very thoroughly into the literature, and gives a bibliography from which it appears that 28 examples, including his own, have been recorded. This bibliography, however, does not include the cases of Keevil, Liggett and my own, which were all reported just before Torpin's article appeared. The number of cases recorded up to the end of 1943, therefore, is 31. The object of the present paper is to record another instance, which came under my charge in March 1945.

Before giving details of my 2nd case it will be of interest to recall some of the points in the histories of the cases already recorded.

In 18 out of 31 patients there was a history of respiratory trouble, in some of acute onset, in others of a chronic character. In 5 the onset of symptoms coincided with the strain of labour. In 2 there was the history of a fall. One occurred after labour during the course of typhoid fever. Torpin refers to the "special tendency to muscle degeneration in typhoid fever and influenza." By far the commonest preceding complication is cough. I drew attention to this in my previous paper, and it is amply confirmed in the literature now studied.

Of the 31 patients, 3 were primigravidae, and 24 were multigravidae, the parity not being stated in 4. Multiparity is therefore a distinct aetiologic factor. In 20 cases the onset of symptoms occurred after the 30th week of pregnancy. The stretching of the rectus muscles over the enlarging uterus must therefore play a part.

The difficulty in arriving at the true cause of the symptoms is shown by the fact that in only 8 of the 31 cases was the diagnosis of rupture or haematoma of the rectus muscle made before operation. The other diagnoses ranged through accidental haemorrhage, twisted ovarian cyst, ruptured uterus, pedunculated fibroid, ruptured hydatid of abdominal wall, ruptured liver, appendix, extravasation of urine, hypernephrosis, to no diagnosis at all, the true condition being revealed at laparotomy.

The treatment in 20 cases was operative, with evacuation of the clot and ligature of the bleeding vessel when found, though in many cases a definite bleeding point could not be found. In 4 cases Caesarean section was carried out. In 4 treatment was conservative, and in the others it was not stated.

Four of the patients died. In Torpin's table relating to 28 cases, the ultimate out-

come to the mother is unstated in 6. Four maternal deaths out of 31 patients, however, gives a maternal mortality of 13 per cent. As Torpin rightly says, this condition must rank in danger with the other haemorrhages of late pregnancy.

The foetal mortality is difficult to estimate, owing to the details being incomplete. There were 3 abortions and 5 stillbirths mentioned in Torpin's table. One patient died undelivered. Three others were delivered at the 7th month, including 1 set of twins. It can be safely stated that the foetal mortality-rate is high.

The Present Case.

The following is the history of my 2nd case of rupture of the rectus abdominis muscle.

Mrs. S., aged 34, 6-para. Five children were born spontaneously at term, including 1 set of twins. All were alive, the weights being 10, 6, 6½, 9½, and 10 pounds. There was 1 abortion at 4 months. The patient attended the clinic in the 22nd week of the present pregnancy. Prior to the present gestation there was nothing of note in her history, but she stated that she was recovering from a cold. She was booked for delivery at home.

On March 12th, 1945, she was admitted to Mayday Hospital, and was first seen by my assistant. The notes made by him read: "About 33 weeks pregnant. Bronchitis for a week. Abdomen slightly larger in last 2 days. Foetal parts not felt. Cullen's sign present. Uterus extremely tender. Slight loss *per vaginam*. Feels faint. Diagnosis—concealed accidental haemorrhage." I was asked to see her prior to an artificial rupture of membranes being carried out.

I obtained a history of 3 attacks of bronchitis since Christmas, 1944, the last 1 being a week prior to admission. She stated that she had pain in the abdomen with the cough, and that a "long lump came up," which her own doctor saw, and which she located in the position of the right rectus muscle. Later, the pain became severe with coughing.

Examination. Peri-umbilical area much stained with haemoglobin (Cullen's sign). Whole abdomen tender, but gentle palpation of uterus showed it to be softer than would agree with a concealed accidental haemorrhage producing such definite abdominal tenderness. Also tender just below ribs (i.e., at upper end of right rectus muscle). Vertex felt in lower segment. Foetal heart heard.

It was decided to watch events, and meanwhile the patient was put on a rectal drip of saline and glucose, a ¼-hourly pulse and temperature chart was kept, a haemoglobin estimation asked for, and 2 bottles of group O blood were cross-matched. Diagnosis—ruptured rectus abdominis muscle.

The haemoglobin was found to be 49 per cent. Blood transfusion was started. At 4.45 p.m. the pulse-rate had settled from 104 to 84, and she looked and felt much easier. She stated that she had not nearly so much pain as the previous night, and much less than when she came into hospital. Abdomen less tender, and now mostly in the right rectus region.

At 6.0 p.m. she vomited. The pulse-rate rose to 112; she complained of feeling cold, looked shocked, and the picture was typical of an internal haemorrhage. The abdomen was not more tender, and foetal parts could be easily felt in the left side of the abdomen. In view of the deterioration in the condition, operation was decided on.

Under general anaesthesia a right pararectal incision was made. On deepening it, considerable bloodstaining of the subcutaneous tissues was seen, mainly in the umbilical region. On opening the right rectus sheath, large clots were seen between the inner edge of the rectus muscle and the posterior sheath. Fresh and old blood clots of the amount of 30 ounces were removed from the whole length of the posterior aspect of the rectus muscle, extending up to the right costal margin and down to the symphysis pubis. Clots were also removed from the right loin, the hand being passed outwards almost to the level of the iliac crest. To reach this situation the blood must have passed beneath the lower free edge of the posterior sheath of the muscle, and outwards between the peritoneum and the transversalis muscle. After clearing the blood from below the semilunar fold of Douglas, the uterus and some omentum could be plainly seen through the peritoneum, there not being any sign of intraperitoneal bleeding. The right rectus muscle was in the main intact, but its deep surface at the level

of the umbilicus was somewhat broken up, and a branch of the deep epigastric artery was found to be torn and still bleeding. This was ligatured. Another smaller vessel was found higher up, and this was also tied. A large pack was then placed along the whole length of the deep surface of the muscle, the lower end being brought out through the lower end of the incision, which was then closed, with tension sutures placed about every 1½ inches to guard against bursting of the wound through coughing. The patient was very chesty during the operation.

During the next few days the general condition improved, but the cough was very troublesome, much purulent sputum being brought up. Atropine gr. 1/200, 4-hourly, and Transpulmin twice daily were given. Fluids were not taken very well by mouth, and there was some vomiting. The quantity of urine passed during the first 3 days was small, but the significance of this was clouded by the general condition. Intravenous and rectal salines with glucose were given to make up for the poor oral intake.

On March 17th, the 5th day after operation, the woman came into labour, and a stillborn female infant, weighing 3 pounds 12 ounces was delivered, the presentation being a breech. Unfortunately, there was a loss of 58 ounces before the placenta was delivered. Further transfusion of 2 bottles of group O blood was given after cross-matching. Towards the end of this she had a rigor and became very restless. Urinary output practically ceased, only 8 ounces being passed during the next 5 days. A severe degree of jaundice also ensued, and the next 10 days were spent in a fight against anuria due to the incompatible transfusion. The clinical details of her condition during this period will be reported in a further paper. It must suffice to say that after about 10 days, during which she was given 2 further transfusions of Rh negative blood totalling 4 pints, she began to pass urine in increasing amounts, her general condition, apart from the jaundice and the anuria, remaining remarkably good. After a sharp attack of Bact. coli pyelitis, which yielded quickly to sulphathiazole, she made a complete recovery, and was discharged on April 28th, the 47th day after admission. The abdominal incision was firmly healed, and the right rectus muscle appeared to be functioning well. There was no abdominal tenderness.

Summary and Comments.

A case of rupture of the rectus abdominis muscle during pregnancy is recorded, the 2nd example to be seen by me, and the 32nd disclosed in the literature.

In the aetiology, multiparity and the strain on the rectus muscles entailed by persistent cough, play the major parts. Other factors are the strain of labour, trauma such as a fall, and in 1 case muscle degeneration due to general disease. All the cases reported have been in the 2nd half of pregnancy, the majority being within 8 weeks of term. Stretching of the rectus muscles by the enlarging uterus must also be a factor.

The difficulty in diagnosis is shown by the great variety of wrong assumptions prior to operation. In only 9 out of 32 cases was the correct diagnosis made.

In 5 instances Cullen's sign was present. The significance of this sign, if the possibility of haemorrhage into the rectus sheath is borne in mind, is obvious.

The condition carries a maternal mortality of 13 per cent, and a foetal mortality probably in the region of 50 per cent. It must, therefore, rank with the other haemorrhages of late pregnancy in danger to mother and child.

The number of cases reported would seem to imply that the condition is rare. Torpin states that "probably a great number of haematomas of the rectus muscles in pregnancy and labour are small, unnoticed and undiagnosed, and consequently unreported." This is probably true, and it is noticeable in the literature that a number of cases have been diagnosed as "concealed accidental haemorrhage." It is very likely that some cases so diagnosed, and treated by artificial rupture of the membranes, have been delivered and have recovered without the true cause ever having been revealed.

In regard to treatment the literature shows that 21 patients were operated upon, with evacuation of the clot, and that in 3 instances the bleeding vessel was found and ligatured. In 4 of these cases Caesarean section was also performed. Torpin's study of the literature led him to the conclusion that conservative treatment is indicated, the chief of these being early diagnosis, complete rest, and blood transfusions when indicated. Torpin's notes of his own case show that on admission the patient had a normal pulse and temperature, physical findings were quite normal except in the abdomen, where there was a mass the size of a large grapefruit rather firm and tender. He goes on to say that the "correct diagnosis was not made, probably because it was not thought of. The following were considered: ovarian cyst, fibromyoma, hydronephrosis, and finally after ecchymosis of the skin appeared, simultaneous intrauterine and ectopic pregnancy. The condition being not very disturbing she was observed for 2 weeks. After some improvement she was allowed to walk around. This was followed by an increase in pain and the size of the mass. Finally, late in the 2nd week, there appeared an area of extravasation of blood into the skin below the umbilicus, further increase in the tumour, and mild surgical shock with sweating and prostration. Her symptoms indicating severe haemorrhage an exploratory laparotomy was done." Only then was the true cause ascertained.

It seems to me that conservative treatment is only justified so long as the general condition remains good and there is no increase in the size of the tumour or of the abdominal pain. If the symptoms point to increase in haemorrhage, shown by rising pulse-rate, pallor, shock, increase in pain and the size of the tumour, I feel that operative intervention has now become urgent, an opinion which is surely supported by the known mortality of 13 per cent. It must be remembered that the blood can find its way between the abdominal muscles and the peritoneum, where enough can accumulate to be rapidly fatal, or can even rupture into the general peritoneal cavity with the same result. If performed in time the operation will not entail opening the peritoneal cavity, the bleeding vessel may be found and ligatured after clearing the area of blood and clot, or, if it is not found, the bleeding can be controlled by packing the space between the rectus muscle and the posterior sheath. If necessary, the deep epigastric artery itself, which can be found on the deep surface of the rectus muscle about the level of the semilunar fold of Douglas, can be tied. It, or 1 of its branches, will be almost certainly the source of the bleeding. The experience of my 2 cases makes me strongly of the opinion that operative treatment is far more likely to avert a fatal issue than conservative measures, even granted the ease with which blood transfusions can nowadays be given.

The case record is published by courtesy of Dr. O. M. Holden, Medical Officer of Health, County Borough of Croydon, to whom my acknowledgements are due.

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Myasthenia Gravis and Pregnancy

BY

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AND

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THE association of myasthenia gravis and pregnancy has received very little attention in the English medical literature. Considerable research work has been published on myasthenia gravis but there are few recorded cases of pregnancy associated with it. This is no doubt due to the relative rarity of the disease. Indeed, Viets and his colleagues[1] report that of 63,268 admissions to the Boston Lying-in Hospital between 1900 and 1940, only 1 patient with myasthenia gravis was registered. Statistics from hospitals in Great Britain would probably substantiate this ratio.

A review of the literature indicates that since 1935, when prostigmin first became available for the treatment of the disease, the outlook has considerably changed. Where previously it was the practice to recommend termination of the pregnancy because of its adverse effect on the disease, there is no doubt that the consensus of modern opinion is entirely against this procedure. At the end of the nineteenth century Sinkler,[2] Punton,[3] Burr and McCarthy[4] reported cases in which an increase in severity developed during the first 3 months of pregnancy. It was probably not realized sufficiently at that time that the course of myasthenia gravis is characterized by periods of relapse and remission. There is no doubt, however, that pregnancy often does cause profound changes in patients suffering from this disease, and this is probably the reason for the therapeutic abortions which were reported in the early literature. But it is true to say that of the more modern records some period of remission has occurred, either during the later part of the pregnancy or occasionally throughout the 9 months. Von Hösslin[5] concluded that pregnancy had an unfavourable effect on patients and not only was this so during pregnancy but also in labour and the puerperium. He was so impressed that he advised patients who had myasthenia gravis not to become pregnant. In this he was supported by Warrington[6] and Gemmell.[7] Wolff[8] also observed a relapse which began after the 1st pregnancy and became more severe during the 2nd, until it was terminated at the 4th month. Laurent[9] described detailed observations on the effect of repeated pregnancies in a patient. He did not observe any change in the 1st pregnancy but relapse occurred in each of the 5 succeeding pregnancies, 4 of which were terminated by the 6th month. Of 7 patients who had 12 pregnancies, Kennedy and Moersch[10] reported that in 5 pregnancies there was aggravation of symptoms during pregnancy and 4 of the patients improved following termination of the pregnancy or weaning of the child.

Throughout the remaining 7 pregnancies a change in symptoms was not observed. Silverstein[11] reported some improvement in his patient during pregnancy, while Milhorat[12] observed a remission during pregnancy and then a return of symptoms following abortion.

Since the introduction of prostigmin in the treatment of myasthenia gravis in 1935, it has been possible to assess more accurately the question of remission and relapse during pregnancy according to the amount of prostigmin required for satisfactory maintenance.

Tabachnick,[13] who reported the onset of myasthenia gravis in a patient after her 4th pregnancy, observed a relapse during the first 4 months of her 5th pregnancy, but no definite remission during the last 5 months. He noted, however, that her daily requirements of prostigmin were considerably less during the first 4 months of the puerperium. In a series of well documented cases Viets, Schwab and Brazier[1] did not observe any relapse in 4 out of 8 cases during pregnancy and in the other 4 the relapses which occurred were mild, caused no anxiety and occurred mainly in the 3rd to the 6th month. These workers were impressed by the onset and completeness of the remissions, which they described as resembling "the sense of complete well-being experienced after an injection of prostigmin methyl sulphate, as used in the prostigmin test, only prolonged over days and months." These remissions were observed chiefly in the last 2 trimesters. In reviewing the effect of therapeutic abortion, Viets and his colleagues draw attention to the cases reported in the literature, in which the abortion was carried out at the end of the 1st or in the early part of the 2nd trimester and conclude that, if prostigmin therapy had been available, many, if not all, of these abortions could have been avoided.

Labour.

Doubtless because the physiological disturbances in myasthenia gravis were not fully appreciated and because it was erroneously considered that the uterus would fatigue, few patients who became pregnant were allowed to go to term. If they did, they were not allowed to deliver by the normal channels. Thus Gemmell[7] delivered his patient by Caesarean section to avoid exhausting her. Of the few reported cases that have been delivered normally, the rapidity of the labour and the absence of complications have been especially noted (Tilney,[14] Laurent,[9] Viets, Schwab and Brazier,[1] Wilson and Stoner[15]). It is probable that the rapidity of the labour is due to the relatively greater relaxation of the voluntary muscles in these patients. In 1 patient observed by Viets and colleagues extra prostigmin was not required throughout the course of the confinement.

Puerperium.

There is no definite agreement as to the effect of the puerperium on myasthenia gravis. Though Reuter[16] noted after delivery a relapse which terminated fatally, and Laurent[9] a relapse which began 8 days after confinement; on the other hand Goldflam[17] observed in his patient a period of well-being that lasted for 3 months after delivery in each of her 3 pregnancies. Viets and his colleagues[1] found that the remission experienced during the latter half of the pregnancy continued until 3 to 5 months after delivery. They did not observe any abrupt change after delivery in any case and regarded the return of increasing symptoms as the termination of the remission experienced during pregnancy. There is no evidence to support the contention of Stevens[18] that the puerperium is an etiological factor in the onset of the disease.

The Effect of Pregnancy on Myasthenia Gravis.

Although on many occasions the relation of the endocrine glands to the causation of myasthenia gravis has been emphasized, no definite facts have yet been produced which would indicate the exact influence of any hormone on the disease. There is no doubt that female patients often have an increase in symptoms just before the onset of menstruation. There are several reports in the literature in which myasthenia gravis was first observed during pregnancy (Tilney,[14] Grosse,[19] Wolff[8]), yet it is difficult to see how pregnancy could be an important aetiological factor. Considering the large number of pregnancies which occur from year to year, and the relative rarity of the disease, one would expect, if pregnancy were an important factor, a much higher incidence of myasthenia gravis in women. Besides this, many patients who have had several pregnancies have not shown any evidence of the disease until the 3rd or 4th pregnancy (Kohn,[20] Freiberg,[21] Reuter[16]).

There is no evidence that pregnancy precipitates the development of the disease, nor is there, as yet, any proof that the course of the disease is prejudiced as a result of pregnancy and labour.

The Child.

The question of myasthenia gravis being a hereditary disease has been raised from time to time. There is only one recorded case of a myasthenic infant being born of a myasthenic mother. In this case Wilson and Stoner[15] reported the delivery of a male child with the characteristic signs and symptoms of myasthenic gravis. After careful nursing his condition improved and at 5 weeks any evidence of the disease was not apparent. They were unable to detect any evidence of the disease in the 3rd year and assumed that the child was able to eliminate the factor involved once he led a separate existence, though a period of 2 or 3 weeks was necessary for this purpose.

On the other hand 2 cases have been reported of myasthenia gravis in infants of 21 months and 23 months, both of whose parents were normal and in whose family there was no evidence of myasthenia gravis Kawaichi and Ito,[22] Booth[23]). Although there are a few instances quoted in the literature in which therapeutic abortion was performed because of the fear of transmitting the disease to the child, considering the number of normal infants born of myasthenic mothers there is very slender evidence at present that the disease may be transmitted to the child.

Case Record.

Mrs V. T., housewife, aged 28 years, was first seen in July 1942, complaining of tiredness, difficulty in chewing and swallowing and diplopia and drooping of the right eyelid. She had joined the Auxiliary Territorial Service 18 months before. A year ago she began to have diplopia which occurred at varying times but was most often present in the morning. Two months after this she had difficulty in chewing and swallowing and also noticed that she was unable to whistle and smile properly. Her voice became weak and faint when she had been talking for some time. Five months later her right eyelid began to droop. She felt tired and had attacks of nuchal pain which was more marked towards the end of the afternoon. She was married in July 1942, and 2 weeks later consulted her Regimental Medical Officer because of the aggravation of her symptoms. Her work in the A.T.S. did not affect her health and she had no weakness of the arms or legs.

Her previous medical and family history did not contain any significant features. She was discharged from the A.T.S. and was satisfactorily maintained with prostigmin 15 mg. 3 times a day and ephedrine ½ gr. twice a day. She was able to do all her own housework.

In November 1943 she became pregnant, and at the beginning of the 2nd trimester she found that to relieve her symptoms adequately she had to take

60 mg. of prostigmin daily, with the usual dose of ephedrine. She continued on this dose of prostigmin until the end of the pregnancy. In the last trimester she complained of sleeplessness, which was attributed to the effect of the ephedrine, and this was successfully counteracted by 1 gr. of seconal at night.

She was admitted to the Jessop Hospital for Women on August 17th, 1944, and labour commenced spontaneously on the 20th. The 1st and 2nd stages lasted 11 hours and a live female child was delivered normally. The usual dose of prostigmin was given during labour but at the commencement of the 2nd stage prostigmin 2 mg. and atropine 1/200 gr. were given subcutaneously. The uterus contracted well in the 3rd stage and the placenta and membranes separated and were expressed without difficulty. The uterus maintained extremely good tone and no oxytocic drugs were required.

During the first 4 days of the puerperium the daily dose of prostigmin was increased to 90 mg. and on the 5th day reduced to 60 mg., ephedrine gr. 1 being continued throughout. On the 9th day the daily dose of prostigmin was reduced to 30 mg. which effectively controlled her signs and symptoms. She was discharged on the 15th day. For a period of 9 months after delivery her chief complaints were ptosis, variable diplopia, aphonia and occasional dysphagia. This was adequately relieved by taking prostigmin, 15 mg., and ephedrine, ½ gr. twice daily. She volunteered the information that she felt better than before her pregnancy. When last seen in June 1945, that is, 10 months after delivery, she stated that occasionally her voice became fainter but that she had fewer attacks of diplopia and only her left eyelid drooped. She found it necessary, however, to take daily 3 tablets of prostigmin, i.e., 45 mg., with 1 gr. of ephedrine, to control her symptoms.

Discussion.

In the present case an opportunity was taken to observe closely the effects of a 1st pregnancy on a patient who had been suffering from myasthenia gravis for 18 months. Before the pregnancy there had not been any significant variation in her signs and symptoms. The value of the observation was enhanced by the additional objective evidence provided by the varying amounts of prostigmin required to control the signs and symptoms of the disease. Throughout the first trimester her condition was unchanged. About the end of the 4th month there was a mild relapse which continued until term and was adequately controlled by a slight increase in the daily maintenance dose of prostigmin. At no time was there any anxiety regarding her condition and the question of terminating the pregnancy was never raised. This, on the whole, is in agreement with the experience of Viets and his co-workers[1] in 2 of their patients. The labour of 11 hours was uneventful, delivery was spontaneous and, though some fibrillary twitching of her limb muscles was observed during labour, this was attributed to the extra dose of prostigmin which had been administered at the beginning of the 2nd stage. Throughout labour there was no evidence of any exhaustion of the voluntary musculature and at no time was there any indication of inertia or fatigue of the uterus. It is to be noted that the work done by the involuntary muscles of the uterus had not the effect of increasing the signs and symptoms of skeletal muscle weakness.

Although some records describe relapse in the puerperium this was not the experience of Viets and his co-workers.[1] In the present case the transient mild relapse occurred during the first 5 days of the postpartum period, and necessitated a slight increase in the maintenance dose of prostigmin. At no time were there any severe manifestations and by the 5th day of the puerperium the patient's condition was the same as that obtaining in the latter half of the pregnancy.

A definite remission became manifest on the 9th day of the puerperium and continued for 9 months after delivery. The remission was abrupt and definite and the control of the symptoms was maintained

by less prostigmin than was required before her pregnancy. At the time of writing she is now adequately maintained on her pre-pregnancy dose of prostigmin.

The child was normal and was nursed without difficulty for 7 months. In growth and development the baby pursued an uninterrupted course and at no time did it display any evidence of myasthenia gravis.

Conclusions.

1. The literature on myasthenia gravis associated with pregnancy is reviewed.

2. A case of pregnancy in a patient with myasthenia gravis is described in which the chief features observed were a mild relapse in the latter half of the pregnancy and the first 4 days of the puerperium. The labour was normal and a normal child was delivered. A definite remission of signs and symptoms was observed on the 9th day of the puerperium which continued for 9 months.

3. There is no indication that pregnancy, labour or nursing adversely affects the course of myasthenia gravis in a patient treated with prostigmin and ephedrine.

We wish to express our thanks to Mr. Glyn Davies for clinical facilities and access to the patient who was under his care. The expenses of the work were partially defrayed by a grant from the Medical Research Council to one of us (A.W.).

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Notes on the Treatment of Vesicovaginal Fistula

BY

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Infection of the Bladder and Vagina.

To operate on a recently developed fistula, when the tissues are oedematous is to court failure. At least 3 months should elapse from the date of onset to achieve success.

The patient will then require some days of preparation, as the vaginal wall has usually become unhealthy and somewhat sodden from leaking urine.

If there is an infection of the bladder it should be eliminated. To achieve this I conceived the idea of corking the fistula for a few days before attempting to operate; washing out the bladder daily with sterile water; and changing the urinary reaction. By this means, also, the vaginal walls are kept dry, and with daily douches soon regain a more normal condition. For the purpose of "corking" the fistula I use rubber corks of various sizes, filing a neck at the small end in the shape of a stud (Fig. 1).

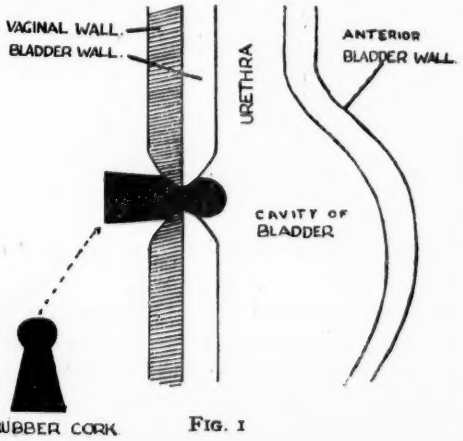

FIG. 1

This cork does not, in any way, injure the edge of the fistula or cause inconvenience to the patient and she need not be confined to bed. It is necessary to impress on the patient the fact that this is only the first stage of the operation as, when she finds that there is no more urine leaking into the vagina, she may imagine that she is cured and ask to be allowed to leave the hospital.

Prolapse of the Mucous Membrane of the bladder into the fistula while it is being stitched may prevent the perfect coaptation of the muscular layer of the bladder thereby causing a leak. To overcome this difficulty I devised the following procedure, which made more certain a perfect operative result. Following the separation of the walls of the vagina and bladder as in a colporrhaphy, I adopt in reverse the method of treating the stump of the vermiform appendix, where, after inserting into the caecum a purse string suture around the appendix stump one pushes the stump into the caecum.

I insert a purse-string suture of fine catgut, as near the refreshed edge of the fistula as possible, leaving it untied and the suture long. Then, passing a sound through the urethra into the bladder and out at the fistula, the free ends of the suture are tied behind the bulbous end of the sound (Figs. 2a and b). On withdrawing the sound, the free ends of the suture now come out at the urethra (Fig. 3). By gentle traction on these ends the edges of the fistula are infolded into the bladder and out of the way, so allowing interrupted stitches to pass

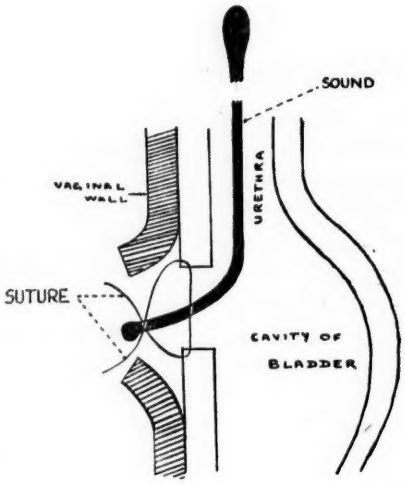

FIG. 2 a.

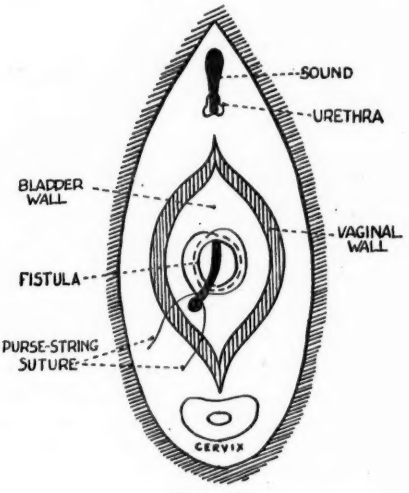

FIG. 2 b

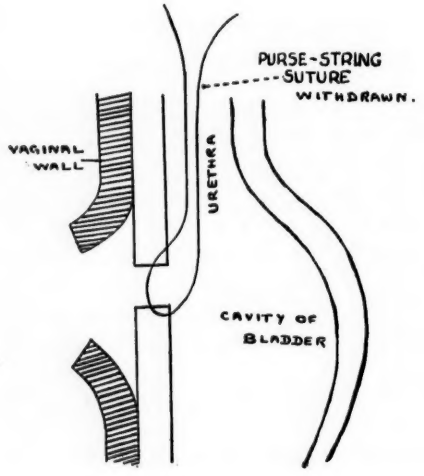

FIG. 3

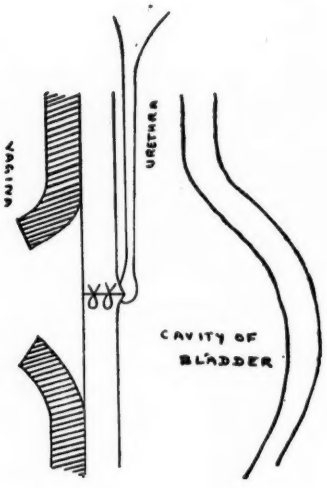

FIG. 4

through the bladder musculature down to, but not through, the mucosa without risking prolapse of the mucous tag, thus accomplishing perfect sealing (Fig. 4). The purse-string suture is then removed *via* the urethra. The vagina wall can then be dealt with as in a colporrhaphy (Fig. 5).

Removal of Blood Clot from the Seat of Operation.

In all operations for vaginal repair the presence of blood clot, no matter how small the amount, at least retards, if it does not entirely prevent perfect union.

The use of swabs has not only the dis-

advantage of wasting time and disturbing the continuity of the operation, but also the act of swabbing is bound to injure the tissues, even to a slight degree, which is detrimental to a good result.

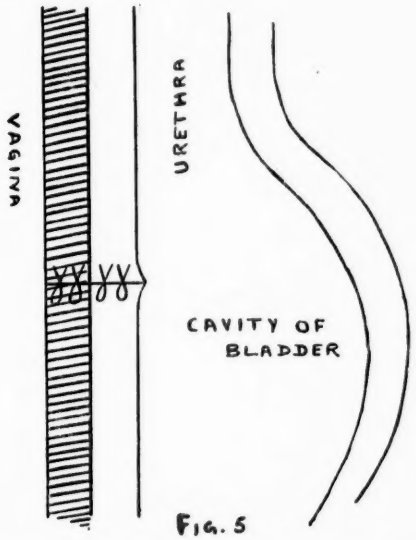

FIG. 5

I have, therefore, for a long time given up their use in all vaginal operations and work entirely under running sterile water. The douche stand is placed in such a position that the nurse, detailed especially for the purpose, and standing beside me, can keep up continuous irrigation over the seat of operation. A good nurse soon learns to regulate the strength of flow to suit the stage of the operation, thereby becoming an important member of the surgical team. There is no doubt that the healing process following under water operation is quicker and better; the patient also has a much more comfortable convalescence.

After Treatment.

It is not necessary to subject the patient to the discomfort of self retaining catheters, or to vaginal packing.

If the patient is nursed on her back for 3 or 4 days and catheterized with a soft rubber catheter every 4 hours for the first 48 hours, and then every 6 hours for the following 4 days, she can then micturate normally without any fear of doing harm to the newly healed tissues. If, however, the act is found impossible, as so often happens in repair operations catheterization night and morning will be found sufficient, until the patient is allowed up on the 14th day, when there will be no difficulty.

Vaginal Packing.

This is unnecessary, in fact, like swabbing it may endanger the vaginal stitches, and if they give way the bladder loses its chief support.

Lawson Tait*

BY

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TO-DAY we celebrate the hundredth anniversary of the birth of Lawson Tait—a great surgeon and a great personality. Tait was the son of Archibald Campbell Tait, a writer to the signet, who practised in Edinburgh and who was a cousin of Archbishop Tait of Canterbury. Perhaps I should have said "reputed son," for there is a doubt as to Tait's parentage. Tait was born on May 1st, 1845, in Edinburgh, and was educated at Heriot's Hospital, one of the great schools which have contributed so much to Scottish education. Tait underwent his medical education in Edinburgh, and there he came in close contact with James Syme and J. Y. Simpson, for both of whom, as men and surgeons, he had great admiration. He obtained the conjoint qualification of the two Royal Colleges of Edinburgh in 1866, and in 1867 was appointed House Surgeon to Wakefield Infirmary. It was in Wakefield that he met the lady whom he married, his marriage taking place in 1871. While at Wakefield Tait performed ovariotomy 5 times. Things must have been different then from what they are now, for it is difficult at the present day to imagine a house surgeon performing abdominal operations which his chiefs would shrink from doing. That he did this is proof of that courage which was one of the outstanding features of Tait's surgical career for, to quote his words, "The results of ovariotomy I have seen in Edinburgh were truly awful—some 30 cases and not a recovery."

That at that time Tait's interest was not only in the surgery of the abdomen is proved by the fact that in 1870 he wrote a pamphlet—he loved writing pamphlets—on the treatment of cleft palate. His method of treatment is described with that clarity which characterized all his surgical writings, and his methods anticipated in important particulars the work of Arbuthnot Lane in our time. Tait wrote on cleft palate 75 years ago, and he did not leave much unsaid. There is the same "complete" note about Tait's description of cleft palate and its treatment as there is in Brodie's description of chronic bone abscess and in William Hey's description of injury to the internal semilunar cartilage of the knee.

Tait came to Birmingham in 1870, purchasing the practice of Dr. Partridge in Lozells Road, and there he settled down as a general practitioner. Soon after coming to Birmingham, finding it necessary to add to the income derived from his practice, he became a leader writer on the *Morning News*, a daily paper which had not a long life, but which had the distinction of being edited by George Dawson, a Nonconformist minister, very famous in his day, a man of marked individuality and in whom there was a certain spark of genius.

The practice in Lozells Road did not give scope for Tait's tremendous energy and

* The Tait Oration, delivered on the occasion of the Lawson Tait Centenary Celebration at the Queen Elizabeth Hospital, Birmingham, on June 29th, 1945.

transcending ability, so he took the diploma of Fellow, first of the Royal College of Surgeons of Edinburgh and then of the Royal College of Surgeons of England, and he gave up general practice and started practice as a consulting surgeon. This he did at the age of 26 and without holding a hospital appointment. Courageous as ever! It goes without saying that he realized the necessity of being on the staff of a hospital and so, at his instigation and with the help of Arthur Chamberlain, the Birmingham Women's Hospital was founded. At first this hospital was at No.8 The Crescent, but was afterwards moved to some old premises at Sparkhill. I have myself heard Tait say that the greater part of his work was done in a converted farm-house, and this was the truth. I shall have more to say about his views as to hospitals and their construction rather later. With his membership of the staff of the Women's Hospital Tait's phenomenal surgical career began, a career which is the story of a remarkable sequence of advances in abdominal surgery, which laid the foundations of many surgical procedures which we now look upon as quite ordinary. It is now for me, as the mouthpiece of the hour, to dwell on these achievements of Tait's and to attempt to draw a picture of what surgery owes to him, and of his striking personality.

At the time with which I am dealing the most spectacular and talked-of gynaecological operation was ovariotomy, and I have mentioned that Tait did this operation 5 times while he was house surgeon at Wakefield. Spencer Wells was at that time the man who had a great reputation as an ovariotomist, but his mortality-rate was nearly 30 per cent. Tait put down this high rate—and apparently rightly—to the fact that Wells treated the pedicle extra-peritoneally by the application of a clamp. Keith, of Edinburgh, lowered this high mortality-rate by cauterizing the pedicle and dropping it back into the peritoneal cavity, but this was rather a laborious process for Keith kept searing the pedicle with his cautery for quite 10 minutes. Tait further reduced the mortality-rate by ligaturing the pedicle, this taking a tithe of the time that cauterization took. Anything that saves time in surgery saves life. Tait brought down the mortality-rate for ovariotomy from Spencer Wells's 28 per cent to less than $4\frac{1}{2}$ per cent—a great achievement for those days!

On February 2nd, 1872, Tait operated on a woman whom he had seen in consultation with Matthew Hallwright. The patient had, for a long time, suffered from abdominal and pelvic pain. Tait diagnosed chronic disease of the left ovary and advised laparotomy. This he did and found a left ovary the size of a pigeon's egg with a chronic abscess in its interior. He removed the ovary and the patient was cured. Tate was the first man to make such a diagnosis and to remove a diseased small ovary. His claim that he was the first man to do oöphorectomy raised a storm of controversy, the reason for this being that Trenholme of Montreal, and Hegar of Berlin, during the next 2 or 3 years recorded cases in which they had done this operation and that Tait had not published a record of his case until 11 years after he had operated. Those were days of bitter controversy in the surgical world and it was asserted that, as Tait did not put his case on record at the time, his statement that he did this operation in 1872 was untrue. Apart from Tait's assertion that he did this operation, it may be noted that he was helped at the operation by Bennett May, who confirmed Tait's assertion, and those who knew Bennett May as well as I did never doubted the truth of anything he said. Tait's position as the first surgeon to remove a diseased small ovary seems unassailable. That this operation has often been done

unnecessarily by Tait's imitators does not detract from his fame.

While talking of tumours and diseases of the ovary, it may be recalled that in 1937 Meigs and Cass, two American gynaecologists, described a condition in which a non-malignant fibroma of the ovary may be associated with ascites and hydro-thorax, and called attention to the fact that removal of the ovarian tumour is curative and that the fluid does not re-accumulate. The condition is now known as Meigs's syndrome. It should not be so called, for Tait described the condition in 1891, and related how in such a case he had removed the tumour and the fluid did not re-accumulate. Thus, he anticipated Meigs and Cass by 46 years, so really we should speak of Tait's, not Meigs's, syndrome.

Perhaps one of the most dramatic first operations ever performed was done by Tait in 1883, when he operated for ruptured tubal pregnancy. This is a matter worth dwelling on for a few moments. I think it was some time in 1882 that he saw, in consultation with the same Matthew Hallwright, a woman dying from intra-peritoneal haemorrhage, which Tait diagnosed was due to ruptured tubal pregnancy. Hallwright urged operation. This operation had never been done and Tait was appalled at the prospect of doing it, and did not operate. However, he was a big enough man to consider any suggestion and soon afterwards he saw a similar case with Dr. Spackman of Wolverhampton. He operated and the patient died. Then he saw a case of the same kind with Edward Sutton Page of Solihull. He operated and the patient recovered. Tait, by his courage and skill, had shown how women's lives could be saved when suffering from the effects of a previously considered fatal surgical catastrophe. How simple it all seems now. How clear to us that operation is the only treatment in such cases and that the operation is by no means a difficult one, but it is not in surgery only that it requires the great man to make the simple discovery. If Tait had done nothing else that was notable, his name would go down to posterity for this. Not even his many opponents can deny that he did this operation in 1883, and that he was the first man to operate for ruptured tubal pregnancy.

Perhaps not so spectacular as this, but equally important, possibly more important because the condition is more common, was Tait's work on inflammatory diseases of the uterine appendages. He was the man who insisted that many women were suffering from abdominal pain and ill-health owing to their having inflammation of the uterine appendages, often following gonorrheal infection. In 1877 he opened the abdomen of such a patient and found a pear-shaped swelling attached to the left corner of the uterus. He tapped this with a trochar and withdrew altered blood. He did not remove the swelling, but drained the cavity, diagnosing that the condition he was dealing with was really due to inflammation of the uterine appendages. He went on investigating such cases and a few months afterwards he removed his first pyosalpinx. Hegar had removed a pyosalpinx a few months before Tait did; so had Spencer Wells. Be that as it may, it was Tait who pointed out the frequency of inflammation of the appendages, it was Tait who insisted on operation in such cases, and it was Tait who met with fierce opposition and virulent abuse for this insistence. In this country and America, operation for removal of diseased uterine appendages has come to be known as Tait's operation. It was Tait's senior confrères, men like Spencer Wells, Matthews Duncan and John Williams, who opposed the performance of this operation, and they it was who, with the *Lancet* (August 21st, 1886) thought they could successfully dis-

parage the operation by referring to it as "spaying." In a letter to the *Lancet* Tait dealt with this name for his operation, and he did so in his usual direct and incisive language. No man could speak more plainly, when occasion required. Gradually his more enlightened confreres, as for instance Greig Smith of Bristol and Cullingworth of Manchester, came to support Tait. None admitted more fully than Tait did that the *ardor operandi* of many of his less experienced followers led them to remove the appendages in patients in whom it was not in the least necessary to do so, but Tait cannot be blamed for that.

Tait was furiously attacked for his views on the pathology and treatment of inflammatory diseases of the appendages. Why was he so fiercely attacked by men of the standing of Spencer Wells and Matthews Duncan? I cannot help thinking that a chief cause of their attacking him was jealousy, that jealousy of which quite an able plodder is so often guilty when he is up against a genius. Another cause of jealousy was, it seems to me, that Tait was a provincial surgeon living in the outer darkness of Birmingham. He himself gloried in this and never seemed inclined to move his headquarters to London. Patients came to Birmingham to consult him from all over the world—and that was enough for him. As an illustration of Tait's pride in being provincial, perhaps I may be allowed to quote from his account of his American tour in 1884, in which he says that on the library table in the medical school of Harvard University he found "a well-used copy of Mr. Sampson Gamgee's book on Fractures—a fragment of comfort for my provincial soul." Another cause of the attacks on Tait was without doubt his personal characteristics. He was always sure of himself. He knew what a big man he was and that he stood head and shoulders above his attackers. What is more, he did not hesitate to say that he knew this. If he thought a man was a fool, he told him so. This does not make for friendly controversy, more especially when one of the controversialists glories in a fight. These attacks did not disturb Tait. He could be trusted to give more punishment than he took. Tait's work on Inflammation of the Uterine Appendages will, I think, always be looked upon as his *magnum opus*.

In 1879 Tait operated on a patient with an enlarged gall bladder, removing a gallstone and draining the gall bladder, the patient recovering. He thought, and it was generally thought in this country, that he was the first to do this operation, but it appeared that cholecystotomy was done in 1867 by Blobbs, who was Professor of Surgery in the University of Indiana, U.S.A. However, Tait was the first man in Europe to do it, and he must be looked upon as the pioneer of gall-bladder surgery.

During the early part of Tait's surgical career Lister's system of antiseptic surgery was in course of evolution, supported by most surgeons, vehemently opposed by others, as for instance Savory, perhaps most vehemently of all by Tait, who claimed that he obtained as good results regarding wound treatment as did the Listerians with their tremendous attention to detail and the frequent dressing of their wounds. Tait would not let any chemical get near his wounds. He cleaned his instruments by pouring boiling water over them, and after a time he had the water with which he washed out the peritoneal cavity boiled. He was very fond—too fond to my way of thinking—of washing out the peritoneal cavity. I have heard him say that for this purpose he used Birmingham tap water, which, he said, contained "thirty different kinds of beasts." The fact is that Tait would not admit that sepsis of a wound is caused by organisms. Consequently he did not realize that boiling the water used for washing out

acted by killing the "thirty different kinds of beasts." He dressed his wounds with a pad of dry absorbent cotton wool tissue, and he dressed them very infrequently. It does not detract from Lister's great work to say that Tait was, without doubt, the great inaugurator of aseptic, as opposed to antiseptic, surgery, and it is the methods used by Tait that we all now follow. Tait entirely failed to see that regarding wound treatment he and Lister were working along parallel paths. No, he even said, in a pamphlet published in 1883, "I have already seen enough of the so-called antiseptic system of Lister to be able to say that it has been finally dismissed from the Department of Surgery as having done far more harm than good. I venture to predict a similar fate will meet it everywhere else, and I take to myself some credit for having burst one of the largest, best-blown bubbles ever displayed to a surgical audience."

Tait was a great advocate of the small hospital and, as I have said, he did his hospital work in a converted farmhouse. In 1877 he wrote a letter, which created a great sensation, to the Governors of the General Hospital, pointing out the high post-operative mortality, more especially in cases of primary amputation, and put down as the cause of this the presence of so many surgical patients in one building. He urged that the Governors should sell the site of the hospital and build four or five small hospitals just outside the centre of the town. I suggest that Tait's view was mistaken, for he attributed the bad results to the building, not to the men working in it. To illustrate this point, I may say that I myself entered as a student in 1886, 9 years after Tait wrote his letter, and I vividly remember the surgeon for whom I did my dressing operating in an overcoat bespattered with patches of dried blood and pus. I well remember that one evening I was standing in the theatre of the old General Hospital watching one of the surgeons operate on a case of strangulated femoral hernia. I had my hands in my pockets. The surgeon had opened the hernial sac, when he asked me if I had ever felt the edge of Gimbernat's ligament. I answered that I had not, and he said: "Feel it now." How well I remember taking my hand out of my pocket and passing a finger into the hernial sac. I grant that the General Hospital Building in Summer Lane was out of date, but surely Tait was mistaken in the main contention in his letter to the Governors. He should have laid down the bad post-operative results, not to the building, but to the men working in it. Tait was on safer grounds when he asserted that hospital buildings should be lightly constructed, preferably on the pavilion system, and that at the end of 30 years or so they should be pulled down and other, similar but improved, buildings erected. He was very insistent on this point.

His membership of the teaching staff of the medical school was short. He was appointed Professor of Gynaecology in 1888 and retired in 1893. I had the privilege of attending his lectures, and my recollection of them is that they were above me—they might easily be that—and that they presumed an amount of knowledge that we students did not possess. Recalling his lectures, I think that they were admirable for the postgraduate; not so admirable for the student.

Tait performed a great service to the profession in 1888. The Medical Defence Union had been started in London in 1885, but was a failure. In 1888 it was refounded in Birmingham with Tait as a very active President, and as a result of his energy the Union at once began to flourish. He gave up the Presidency in 1893, because the profession was angered at the way he spoke of vivisection and its advocates at a

meeting of the Church Congress. He was an ardent, and somewhat irrational, opponent of vivisection. However, he had set the Union on the road to success.

As I have said, Tait was satisfied to retain his consulting room and nursing home at No. 7, The Crescent, and it is not going too far to say that, while he was at the height of his fame, No. 7, The Crescent, Birmingham, was one of the most famous spots in the surgical world. Men came from America and most European countries to see Tait's work; such was his fame.

Tait's interests were not purely medical. In 1886 he was a candidate for Parliament, fighting the Bordesley Division of Birmingham as a Gladstonian Liberal, but he was unsuccessful. He was for some years a member of the Birmingham Town Council, doing most of his work on the Health Committee and writing various pamphlets on refuse-disposal, housing etc.

Tait matured early. We have seen that he did abdominal operations when he was 24 years old. His great original work was finished by 1890, when he was 45. He went on practising and writing, but his work after 1890 was not epoch marking, as it previously had been. He died in 1899, when he was 54.

In appearance Tait was striking: he was short, massively built, with a large head. He was a man who would be noticed anywhere. He used to drive about Birmingham in a victoria drawn by a pair of dapple greys, and it is said that he always had four pairs of these horses. He used to wear a soft wideawake hat and a short jacket, usually of velvet. He insisted on Christopher Martin, then his assistant, wearing a tall hat and frock coat. Martin asked him why he did so and why he would not let him wear a soft hat and short jacket. "Because" Tait answered "you are only Christopher Martin but I am Lawson Tait." A stranger seeing Tait in his carriage could not fail to ask "Who is that?" Tait had a beautifully modulated voice and a very sweet smile, but he could, and often did, burst out suddenly into a furious rage. It is said that on one occasion—it was in the early days of the telephone—he kept getting wrong numbers or something of that kind, and he broke out into one of his tempers. He seized the telephone apparatus, tore it from the wall, threw it to the floor and literally danced on it, smashing it to pieces. Doubtless he felt much better after doing this. He could, when irritated, show a pretty sarcasm. As an example I will quote a story which I have myself heard him tell. He had been called into the South of England and had operated on the wife of a very rich man, who asked Tait his fee. Tait named a large one, "too large" the husband said. Tait answered: "Well, on one page of my fee book I put the name of the payer and the sum paid. On the opposite page I put the names of defaulters. I do not care which page your name appears on, but it is going to appear on one of them." I need hardly say that Tate received his fee.

Tait was a peculiar man of uncertain moods. He told me that he had once been called to Liverpool and had received a large fee, the whole of which he spent on carved ivory figures before entraining for Birmingham. He was a collector of these and other curios, but not a very discriminating collector, and I am afraid had many shams passed off on him. He was fond of entertaining, more especially of giving large dinner parties. Sometimes these dinners were fit for a king; sometimes, well not quite so good. With all his occasional bad tempers, with all his high estimation of himself, Tait was at heart a very kind man. He took many patients into his nursing home and operated on them without charging a fee. I must ask forgiveness if I strike a personal note. Tait and my father were enemies and

never spoke to each other. Why, I do not know. Yet, when first I became a member of the staff of the General Hospital and started in practice, Tait was a great friend to me. He was too big a man to bear a grudge and to remember old enmities.

Tait, as I have said, had many enemies, some of whom attacked him fairly, others unfairly, the chief mode of attack of the latter being to assert that his statements as to his work were untrue. As regards his *magnus opus*, i.e. his investigation of and his operation for inflammation of the uterine appendages, Tait admitted that pathologists had for a long time described the condition, but then apparently came a full stop, for the clinicians before Tait's time failed to recognize these cases and had failed in their treatment of the patient. At the International Medical Congress in 1881 Spencer Wells came out with his famous piece of criticism regarding these cases: "It is very extraordinary that so many such cases should occur. I have seen only one in my lifetime. Perhaps they all go to Birmingham." Surely we know now that Tait was speaking the truth: present-day experience proves that. No, it was not that Tait was untruthful, but that his accusers did not appreciate the clinical symptoms and signs shown in these cases: while treating these women, who were often reduced to chronic invalidism, they played about with pessaries and douches, while Tait, who made an accurate diagnosis, removed the appendages and cured his patients. The question arises: were these older gynaecologists clinically ignorant or were they all-knowing and Tait untruthful? There can, I suggest, be only one answer. Tait was speaking the truth and was working on the right track. But these battles are of the past and we of our time all recognize Tait's work in this sphere of surgery.

Tait was a great clinician. In questioning and examining a patient he was quick and aimed straight at the centre of the problem, brushing aside the extraneous. He had clinical intuition developed to a remarkable degree. I have seen him operate: he made a small incision through which he introduced two fingers, and by touch alone he made out the condition with which he had to deal. He was a marvel at separating adhesions. I have heard him say that he gained this skill by practising peeling oranges. He was a very quick operator. I once saw him open an abdomen, remove two ovarian cysts to which coils of intestine were densely adherent, and the patient was back in bed 20 minutes after the incision was made. While he operated there was absolute silence. Watching him operate made one think that it was all so easy, surely a supreme proof that the operator is a master. It is interesting to recall that he never operated in an operating theatre, but always in the patient's bedroom, the patient lying on a simple wooden trestle table.

Tait was the Napoleon of surgery—clear thinking, courageous, original, inventive, not bound by any precedent. He was a man of many facets, and that he was a surgical genius there is no doubt. With the modern developments of abdominal surgery there is a tendency to forget the man who, by the brightness of the lamp he lighted, showed the way. He dispersed once and for all the fear and trepidation with which surgeons before his day opened the peritoneal cavity. He simplified abdominal surgery. He was one of the greatest surgical originators and pioneers of modern times. Birmingham must always be proud that Tait was one of her citizens and that it was here that he did his wonderful work.

BOOK REVIEWS

"Midwifery for Nurses." (Thirteenth edition). By HENRY JELLETT, B.A., M.D., F.R.C.P.I. Consulting Gynaecologist, Rotunda Hospital Dublin; late Consulting Obstetrician to the Department of Health, New Zealand, etc. 1945, 456 pages. London: J. & A. Churchill, Ltd. Price 12*s*. 6*d*.

THIS is intended to be a textbook for the pupil-midwife. As such there is a fairly well defined range of subjects which must be covered, and this is done. The subject matter is clearly set out as would be expected of so eminent an author and teacher. Emphasis is rightly laid on the normal, which will constitute so large a portion of the midwife's work. Methods of examination are well described, and the importance of abdominal examination is stressed. The description of the physiology and management of normal labour leaves little to be desired, while there is an excellent chapter on asepsis in midwifery. The preparations to be made for the conduct of labour are clearly detailed. Not only will the midwife in training find this of value, but even established and experienced midwives could study this chapter with profit.

It is surprising to read, however, that "obstetrical anaesthesia" induced by a well-trained nurse using chloroform or ether is considered permissible. The Royal College of Obstetricians and Gynaecologists condemned their use in its carefully considered report on the subject. Recent correspondence in the medical press has shown quite clearly that great improvement is still necessary in the administration by midwives of gas and air for analgesic purposes. Lack of understanding of the principles of analgesia, lack of interest or want of ability, among practising midwives, to maintain in order simple apparatus has been demonstrated. It would seem that the College was correct in advising against the use, by midwives, of these poisonous substances.

Abnormal presentations are so presented that the pupil-midwife can form a clear mental picture of what is happening as the child is born or as labour comes to an *impasse*. But the description of antepartum haemorrhage is spoiled by the prominence given to the making of vaginal examinations, the rupturing of membranes and plugging of the vagina—all of which are contemplated as being done by the midwife if she cannot obtain medical aid. Nowadays the medical practitioner who makes vaginal examinations on cases of antepartum haemorrhage, before sending them into hospital, is criticised. Why tell the pupil-midwife to do something which no hospital is prepared to teach her to do, which she is most unlikely to do adequately, and for which even the skilled medical practitioner requires the administration of an anaesthetic? Has not the time come when this teaching should be revised?

It may be objected that these are matters of opinion. But conservatism in teaching may be persisted in to such a degree that the teaching becomes out of date. This is seen on the chapter dealing with puerperal sepsis. Here we find, laboured at length, a distinction between sapraemia and septic infection. An attempt is not made to explain that the mode of infection, the signs and symptoms, and responses to treatment may vary according to the organism responsible for the infection. The streptococcus is the streptococcus—no differentiation is made between haemolytic streptococci and anaerobic streptococci. Turning to treatment it is astonishing to read that "as a rule, the first step in the treatment is to obtain some of the discharge from the uterus for bacterial examination, *as injections of a vaccine prepared from the same type of organism as that with which the patient is infected or of a serum*

sometimes prove of great value and are usually tried" (reviewer's italics). It is equally astonishing to learn that " of the many different remedies which have been suggested for the cure of a general infection it is probable there is none so effective as good nursing." This is frankly untrue. Septicaemia due to the *staphylococcus aureus* was almost invariably fatal, irrespective of the quality of the nursing, prior to the introduction of penicillin. Penicillin is not even mentioned. This whole chapter largely requires to be rewritten.

The chapter on obstetric operations is poor even for a nurses' textbook. It may be Dr. Jellett's practise to induce labour by bougies or the stomach tube in cases of contracted pelvis, but others may doubt whether it is " the best method." Must the vertex present before the forceps can be applied with safety? Why not the face, or the after-coming head? Is Caesarean section really so unimportant to the nurse that it can be dismissed in 4½ lines, while 7½ are devoted to pubiotomy?

The section dealing with the normal and abnormal infant is adequate though sketchy in parts.

The book ends with a number of valuable appendices dealing with cancer of the uterus and breast, obstetrical outfits, prevention of sepsis, antenatal and postnatal exercises, and general information and recipes. The book is of suitable size, well bound, on good paper, well printed and illustrated. That this book has appeared regularly for '44 years is a tribute to its worth. It certainly deserves to be kept up to date. In spite of all its good qualities some portions of this latest edition still require much further revision.

ANTHONY W. PURDIE.

" A Textbook of Pathology of Labor, the Puerperium and the Newborn." By CHARLES O. MCCORMICK, A.B., M.D., F.A.C.S. Clinical Professor of Obstetrics, Indiana University School of Medicine. 1944; 399 pages. London: Henry Kimpton. Price 37*s*. 6*d*.

THE scope of this book is limited to the consideration of labour, the puerperium and the new-born child. Pregnancy is excluded. It is based on the lectures given by the author over a period of 25 years to senior medical students of his own university.

The field covered is wide while not exhaustive. An attempt is made to set out the essentials of present-day obstetric thought, avoiding as far as possible controversial matter and theoretical discussion. Therefore neither in its scope nor in manner of its presentation can it be regarded as a complete obstetrical textbook for the medical student. Yet it is not a cram-book. It contains a great amount of factual matter, presented in a didactic manner, with unmistakable emphasis on important points. Throughout the text clarity and brevity are the dominating features. As far as is possible tabular presentation of material is used, sentences are often not completed while the second person is used in describing therapeutic procedures. There is efficiency but with hustle. The liberties taken with the language would be deplored by the grammarian and by those to whom style in writing is still a matter of moment.

The subject matter is sound. There might have been a little amplification of the reasons for deciding on certain therapeutic measures, while a little less detail in description of some operative techniques would not have mattered. The student is not going to do Caesarean sections without further training and wider reading, but he may well have to look after a case of eclampsia. He would therefore be interested to know, in more detail, why Caesarean section is sometimes employed in eclampsia with a mortality of 30 per cent to 40 per cent, while conservative treatment may result in a mortality of not more than 10 per cent. But he will not be interested in the description of three different methods of performing extra-peritoneal Caesarean section. One might question the wisdom of yielding to the demand of husband and wife for sterilization at the first Caesarean section, done on a healthy woman for contracted pelvis. For all that the subject matter is sound and up-to-date.

The book is well printed, easy to read, beautifully and clearly illustrated—in fact the text is sometimes superfluous, so fine are the illustrations.

The student who uses this in conjunction with his clinical teaching may acquire a sound knowledge of the field covered. The practitioner may turn to it in a hurried moment and find a clear authoritative direction. The specialist will be less interested, but may glean some new ideas for the presentation of his subject. The book closes with

50 obstetric aphorisms ("gathered from here and there") which all could read with interest and, perhaps, with profit.

ANTHONY W. PURDIE.

"Recent Advances in Obstetrics and Gynaecology." By ALECK W. BOURNE and LESLIE H. WILLIAMS. 6th edition, 1945. London: J. and A. Churchill.

IT is a pleasure to welcome a new edition of this volume, which has for nearly 20 years presented all that is best in current work in the 2 subjects. Here is a volume packed full of factual information, including much that is truly recent, and which admirably achieves the aim of the authors, set out in the preface, to give not only lists of references to recent papers, but also to indicate and crystallize the general trend of thought along various lines.

The authors are fortunate in having again secured the collaboration of Mr. Wilfred Shaw, who contributes an excellent chapter on Ovarian Tumours, and helps to clarify a difficult subject. Dr. Rohan Williams has revised his chapters on Radiology in Obstetrics and on Radiological Investigation and Diagnosis in Gynaecology, and gives a particularly useful description of the methods of X-ray pelvimetry and of the classification of pelvic types. Dr. W. M. Levitt has contributed a full account of modern views on the Radiotherapy of Gynaecological Disorders.

This book contains much material which has appeared in earlier editions, and which is rightly regarded as authoritative. In addition there is much new material, summarizing advances over the past 20 years in such important subjects as Nutrition in Pregnancy, Vitamin K, Stillbirth and Neonatal Death and Erythroblastosis. The chapter on Erythroblastosis gives perhaps an over-simplified account of a matter which is becoming daily more complex. Little mention is made of the subgroups of the Rh factor or of incomplete antibodies, but these are minor omissions which will doubtless be remedied in future editions when more work has accumulated on this subject.

In a book which deals with so many matters of perennial and topical interest it is difficult to select any part for special mention. The chapter on Cancer of the Uterus is already well known as a comprehensive account of the relative merits of the different forms of treatment available. A very full account is given of the investigation and treatment of sterility and the section on Leucorrhoea includes important original work on chronic cervicitis. The chapter on Sex Hormones summarizes recent knowledge on the chemistry, physiology and therapeutic applications of these substances.

This is a book, then, which is an invaluable addition to the library of all who are practising obstetrics and gynaecology and one which should prove particularly useful to those studying for higher examinations in these subjects. The authors are to be congratulated on this latest addition to the literature and on the excellent balance of views which is maintained throughout.

"Précis d'Obstétrique." By FABRE. Volume II. Abnormal Obstetrics. 8th edition. 1940. Paris: Librairie J. B. Ballière et Fils.

THE 8th edition of Fabre's "Précis d'Obstétrique" was published in 1940. It is 1 of a series of 48 volumes, designed for students working for the Doctorate of Medicine.

It is a little difficult to appraise a work produced over 5 years ago, but it must be admitted that there is a good deal in this volume which would not meet with the approval of most British obstetricians.

It is surprising to find the main alternatives for the treatment of placenta praevia before labour to be plugging the vagina or digital dilatation of the cervix, followed by bipolar version, while Caesarean section is reserved only for primipara where resistance of the cervix prevents the latter manoeuvre. De Ribes' bag—now largely out of favour in this country—receives considerable attention.

Mention is not made of the use of the Aschheim-Zondek and other pregnancy tests in the management of abortion or in the diagnosis and after treatment of hydatidiform mole.

The section on pregnancy toxaemias is confused. Mention is not made of the role of vitamin B in hyperemesis. Albuminuria and eclampsia are dealt with as entirely separate and disconnected conditions, and in neither section is any reference made to the blood-pressure, either in diagnosis or as a means of observing the progress of these conditions.

A detailed and most interesting account is given of the gross deformities of the pelvis, associated with general skeletal diseases and the impression is gained that osseous disease, such as tuberculosis and rickets, is a good deal more common in France, particularly as a cause of pelvic contraction, than in this country. In the management of contracted pelvis trial labour is not mentioned, though pubiotomy is favoured as a method of dealing with difficult labour due to this cause.

In the section dealing with forceps delivery, rotation by means of the midwifery forceps is advocated in cases where the occiput is not anterior, while manual rotation receives no description.

In post-partum haemorrhages hot douches and bimanual compression are favoured while ergotine and ergotinine are recommended as oxytocics—ergometrine and posterior pituitary extract are not included. Sulphonamides are not prescribed in the treatment of puerperal sepsis, though it is probable that this has been altered since this volume was written and that sulphonamides, and penicillin, which is now being produced in France, are used.

These criticisms serve to emphasize the differences in obstetrical practice between those in Britain and their French colleagues. The impression is gained that in France, midwifery is more conservative than in this country and that there is less tendency to resort to Caesarean section as a solution of obstetrical difficulties.

The book is admirably written and is notable for the clarity with which the author's views are expressed. The illustrations are excellent and numerous.

JOSEPHINE BARNES.

"Obstetrícia Prática." By L. A. HORTA BARBOSA, Reader in Clinical Obstetrics and Gynaecology in the Faculty of Medicine of the University of Brazil. Second edition; 518 pages with 341 illustrations. Price Cr$. 250,000. Rio de Janeiro, Brazil: Edicoes Medicas da Editora Scientífica. 1945.

THIS book, the first treatise on midwifery from Latin-America reviewed by this journal, was awarded the Mme. Durocher Prize of the National Academy of Medicine of Brazil on its appearance in 1940. Mme. Durocher was the first female diplomate in obstetrics of the Faculty of Medicine in Rio de Janeiro, in 1834, and the only woman ever elected to the membership of the Academy. She appears to have been a doctor who was able successfully to invade the province of the midwife in her adopted country (she was of French birth), and this book seems to have well deserved the award made in her name as it is intended for students and for those practitioners who must work without assistance in the remote rural areas of vast Brazil.

The author has been deeply influenced by his friend and mentor, Professor Fernando Maghalães, whose recent death has deprived South America of a great teacher. The book is dotted with phrases or whole paragraphs from Maghalães' admirable *Síntese Obstétrica*, and these have the quality of memorable simplicity that marks some of the utterances of Smellie, Harvey and Miles Phillips. The reviewer was led by Dr. Barbosa's many references to read *Síntese Obstétrica* and considers that it deserves wider examination in this country.

Dr. Barbosa's method is clinical and practical and limited to a description of signs, symptoms and treatment with the minimum of discussion of aetiology and laboratory diagnosis. He adds up for his readers the features of the clinical picture until an entity is produced and then applies a set, sound line of treatment. The very few methods of laboratory diagnosis are described in great practical detail so that the rural practitioner with the most rudimentary means may apply them.

The mechanism of labour is well and vividly described and illustrated. Adverse criticism may be here introduced, however. The wearing of a face mask by the accoucheur is not mentioned. It is possible that the climate of Rio de Janeiro does not favour the harbouring of pathogenic organisms in the upper respiratory tract but this is an omission that cannot be overlooked. The only antiseptic described is the somewhat outmoded oxyanurate of mercury (1 : 1000).

Too, drastic purgation is prescribed in pre-eclampsia; and tamponade of the vagina, repeated if necessary, is the advised treatment in placenta praevia, with Caesarean section as a second choice if tamponade fails, and the application of Willett's forceps is rather deprecated!

In the treatment of puerperal sepsis, too little mention is made of bacteriological diagnosis,

although this is probably deliberately done because of the limitations of the readers for whom the book is intended, and it is a little odd in this epoch to hear of vaccino- and proteino-therapy and the intrauterine application of iodin-creosote-glycerin as useful therapeutic measures.

In pyelitis of pregnancy a 6–8 g. daily dose of sulphanilamide is recommended with reduction of fluid intake!

But analgesia and anaesthesia in labour are well described and the note on local anaesthesia could not be bettered.

In the section on obstetric operations it is a pity that a book like this with its avowed range of readers should include an illustrated description of trachelotomy and vaginal hysterotomy, and this is a criticism that may well be extended to similar textbooks of midwifery by other authors. The chapter on the obstetric forceps and breech delivery is very well done and the indications for Caesarean section wisely summarized in another quotation from Maghalães as: "all dystocias which are impossible of solution by other means."

Resuscitation of the newborn assumes a more vigorous character than we are accustomed to practise in this country, stress being laid on the methods of artificial respiration now largely abandoned here.

In all, this is a well-written book, worthy of its purpose and the popularity it enjoys in the country of its origin.

MEAVE KENNY.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

D.R.C.O.G. EXAMINATION, OCTOBER 1945.

The following candidates satisfied the examiners for the DIPLOMA of the College:

Dirk Walter Bentinck.
Kenneth Joseph Robson Cuthbert.
Ada Inez Date.
Ann Donnelly.
William Donovan.
Mary Downey.
Mary Muriel Essex-Lapresti.
Margaret Fitzherbert.
Stanley Frederick Hans.
John Ormerod Harrison.
David Worsley James.
Philip Seukaran Jaikaran.
Gordon Trevor Johnson.
John Campbell Miller.
George William Mills.
Marjory Beatrice Morton.
David Charles Mundy.
Diana Joyce Myott.
James Raymond Owen.
Ada Violet Victoria Parkes.
Anthony John Partridge.
Stewart Sandeman Favell Pooley.
David Prysor Jones.
Otto Arnold Schmidt.
Victoria Marie Diana Nicoresti Shaw.
Laurence Spencer Stephens.
Charles Edward Riddiough Wood.
Geoffrey Worden.
John Harley Young.

INDEX TO CURRENT LITERATURE

In this Index an endeavour will be made, so far as conditions permit, to maintain an up-to-date record of all titles bearing on obstetrics and gynaecology and the infant. The classification aims at making immediately available for the reader the titles under the various headings. In the majority of instances the title is obtained from the original publication. Where this has been impossible, the title has been obtained from the abstracting journal shown in brackets. Reprints will be welcomed and should be sent to the Editor.

Any inquiries should be addressed to Miss D. F. Atkins, British Postgraduate Medical School, Ducane Road, London, W.12.

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ANATOMY

1. "The two main diameters at the brim of the female pelvis." C. Nicholson." *Journ. Anat.*, July 1945, LXXIX, 131–5.

PHYSIOLOGY

2. "Normal physiological douches." K. J. Karnaky. *Amer. Journ. Surg.*, July 1945, LXIX, 107–15.

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4. "Studies on the biology of the cervix." M. Barton and B. P. Wiesner. *Irish Journ. Med. Sci.*, August 1945, 6th series, 567–75.

5. "'La buena y la mala gráfica del histerotonógrafo de Frey.' Comentario." (Remarks on "The use of Frey's hysterotonograph.") C. G. Funcasta. *Rev. Españ. Obstet. y Ginec.*, June 1945, II, 433–4.

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PREGNANCY

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13. "Relationship of maternal weight gain and weight of newborn infant." J. S. Beilly and I. I. Kurland. *Amer. Journ. Obstet. and Gynecol.*, August 1945, L, 202–6.

14. "Relation between gastric acidity and the anterior-pituitary-like hormone content of urine in pregnant women." S. Way. *Brit. Med. Journ.*, August 11th, 1945, II, 182–4.

15. "The circulation of amniotic fluid." W. F. Mengert and J. W. Bourland. *Amer. Journ. Obstet. and Gynecol.*, July 1945, L, 79–83.

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Nutrition

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26. "The importance of prenatal diet." J. Warkany. *Milbank Mem. Fund Quart.*, January 1945, XXIII, 66–77. (*Bull. Hyg.*, June 1945, XX, 339.)

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31. "La capilaroscopia en las toxemias de embarazo (con especial referencia al diagnostico diferencial.)" (Capillaroscopy in the toxaemias of pregnancy, with special reference to differential diagnosis.) A. M. Gimeno and F. Orengo Díaz del Castillo. *Rev. Españ. Obstet. y Ginec.*, July 1945, III, 15–27.

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Placenta praevia

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Association with disturbances of the reproductive system

43. "Mioma y embarazo. Conducto clínica." (Treatment of myoma in pregnancy.) D. J. Vandrell. *Rev. Españ. Obstet. y Ginec.*, July 1945, III, 37–50.

44. "Sobre un caso de carcinoma de cuello y embarazo." (Carcinoma of the cervix and pregnancy.) J. R. Picon. *Rev. Españ. Obstet. y Ginec.*, May 1945, II, 343–54.

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Association with infections

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55. "Pregnancy and tuberculosis. Abortion as a therapeutic measure." (Meeting of the Tuberculosis Association, May 11th, 1945.) J. E. H. Roberts, *et al. Tubercle*, July/August 1945, XXVI, 128.

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57. "Tuberculin testing of pregnant women." M. J. Seid. *Amer. Rev. Tuberc.*, June 1945, LI, 537–8.

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LABOUR

Normal

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Abnormal

62. "Estimation of the work of obstetric labor and its significance in heart disease." J. J. Sampson, E. M. Rose and R. Quinn. *Amer. Journ. Obstet. and Gynecol.*, June 1945, XLIX, 719–34.

63. "Complicated knot of the cord." E. C. H. Schmidt. *Amer. Journ. Obstet. and Gynecol.*, July 1945, L, 116.

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78. "Cesarean section under fractional spinal anesthesia." W. Levine, *Amer. Journ. Obstet. and Gynecol.*, July 1945, L, 75–8.

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Lactation

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Abnormal

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Infections

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THE INFANT

General

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